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ROENTGEN THERAPY OF ACTIVE RHEUMATIC HEART DISEASE.*

A SUMMARY OF ELEVEN YEARS' EXPERIENCE.

BY ROBERT L. LEVY, M.D.,

PROFESSOR OF CLINICAL MEDICINE, COLLEGE OF PHYSICIANS AND SURGEONS, COLUMBIA UNIVERSITY; ASSOCIATE ATTENDING PHYSICIAN AND CARDIOLOGIST, PRESBYTERIAN HOSPITAL,

AND

ROSS GOLDEN, M.D.,

PROFESSOR OF RADIOLOGY, COLLEGE OF PHYSICIANS AND SURGEONS, COLUMBIA UNIVERSITY; ATTENDING ROENTGENOLOGIST, PRESBYTERIAN HOSPITAL, NEW YORK CITY.

(From the Departments of Medicine and Radiology, College of Physicians and Surgeons, Columbia University, and the Presbyterian Hospital.)

RHEUMATIC fever is a chronic disease, of which the specific causative agent is, as yet, unknown. Its chief menace to health and life is involvement of the structures of the heart. The use of salicylate as a symptomatic remedy in the acute stages has long been accepted practice. Eradication of foci of infection, avoidance of colds and sore throats, and prolonged rest in a favorable environment are the methods of therapy commonly employed.

There are many cases in which activity of the rheumatic state continues over long periods of time, as indicated by low grade fever, leukocytosis and increase in the rate of sedimentation of the red blood corpuscles. Active lesions in the myocardium can be inferred by the persistence of tachycardia and by progressive alterations in the form of the electrocardiogram. For such patients, many months of rest in bed is essential. Some suffer intensely from attacks of cardiac pain.

In three previous communications[4] we have reported in detail the results of the treatment of rheumatic carditis by Roentgen irradiation of the heart. It was pointed out that Roentgen rays exert a favorable influence on various forms of low grade infection. On the basis of changes recorded in the contour of the electrocardiogram,

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it was inferred that the lesions in the heart were affected. The improvement in the clinical condition of many patients shortly following exposure of the heart to the rays, and the relief of pain in a smaller group, warranted the conclusion that the effect exerted was beneficial. The mechanism by which these changes were brought about remained a matter of conjecture; it was suggested that, in some manner not understood, the reactivity of the cardiac tissues was altered.

It is now almost 12 years since the first patient was treated. Further experience, together with 2 favorable reports in the foreign literature,[2,3] have strengthened our conviction that the method is worthy of continued trial. Certainly until a more direct mode of attack upon the cause of the disease is developed, it furnishes an added measure for shortening the required period of invalidism. These notes may be regarded as a report of progress.

Results After 11 Years. We have followed 48 patients with sufficient care to warrant including them in the analysis (Table 1); 36 are living; 12 have died. There was a wide range in the degree of severity of cardiac damage.

TABLE 1.—SUMMARY OF 48 CASES.*

Living	36	*Dead*	12
Result:		*Death* occurred from 6 weeks to 7½ years after first radiotherapy was given	
Improved	25		
Unimproved	3		
Doubtful	8	*Average duration of life* (from this time), 2¼ years	
With cardiac pain:	8	*Temporarily improved*	7
Relieved	6	*With cardiac pain*	2
Duration of Follow-up:		Relieved, 0 (both had aortic insufficiency)	
Less than 1 year	7	*Cause of Death:*	
1 to 3 years	14	Congestive heart failure	7
4 to 6 years	7	Strept. viridans endocarditis	3
7 to 9 years	4	Pneumonia	1
10 to 11 years	4	Not known	1
Number of Radiation Treatments:			
4 to 25, during a period ranging from 1 month to 1¼ years.			
Average number per patient, 9			
Receiving 10 or more, 12 patients			

* We are indebted to Drs. D. W. Atchley and A. F. Anderson, of New York, and Dr. J. W. Coburn, of East Orange, N. J., for referring private patients for treatment.

Patients Still Alive. Of 36, 25 were regarded as improved by treatment; a direct relationship between betterment and therapy seemed apparent. Three were unimproved; in 8 cases, although recovery from the immediate attack ensued, there was no reason to believe that radiation played a rôle. Of 8 patients with cardiac pain, 6 obtained striking relief.

The duration of follow-up after the first irradiation ranged from less than 1 year to 11½ years. Fifteen patients have now been observed for more than 4 years, and 8 for more than 7 years.

The number of treatments given to an individual ranged from 3 to 25 (average 9); 12 cases received 10 or more. About half of the

patients experienced mild radiation reactions. In general, those receiving the larger number of treatments fared best; but this was not an invariable rule.

Patients Who Have Died. Of 12 cases, 7 died of congestive heart failure; 3 of streptococcus viridans endocarditis; 1 of pneumonia; and in 1 case, dying at home, the cause was not ascertained. Seven patients showed temporary improvement. But in 2 who had cardiac pain associated with a large aortic leak, no relief was obtained. Death occurred from 6 weeks to $7\frac{1}{2}$ years after treatment was initiated. The average duration of life, from this time to death, was $2\frac{1}{4}$ years.

Technique of Irradiation. This was described in previous papers and is repeated here, for convenience.

In giving the treatments the following factors were used: 200 Kv. (peak); 0.5 mm. copper plus 1 mm. aluminum filter; 50 cm. target skin distance. The field was made large enough to include the heart, using one field in front and one posteriorly. Approximately 60r as measured in air, without back-scattering, was applied to the front of the chest and from 100 to 125r to the back, depending upon the depth of the patient's thorax. The object was to distribute approximately 60r, as measured in air, throughout the heart area, corresponding to about 1/10 of the old "erythema dose." If there was evidence of a systemic reaction to this dose the quantity of radiation was decreased. The treatments were given at intervals of 2 weeks for 4 sittings. Then a period of 1 to 3 months was allowed to elapse, and the series of 4 was repeated.

Effects of Irradiation on the Heart. Lesions in the heart have been described in laboratory animals and in humans after deep Roentgen irradiation. In our earlier papers [4a,b] we have pointed out that the dosage employed by others to bring about harmful reactions in the myocardium and pericardium has been much larger than that used by us. Only one of our cases has been examined at necropsy after having received irradiation; a brief protocol follows:

Case Abstract. A girl, aged 17, received 9 radiation treatments during a period of 5 months. She died of acute cardiac insufficiency 24 hours after the onset of fulminating, bilateral maxillary sinusitis. Death occurred 1 year and 4 months after the final irradiation. The pathologic diagnosis was rheumatic endocarditis, mitral stenosis and insufficiency, tricuspid insufficiency, cardiac hypertrophy, thrombosis of the left auricle and right auricular appendage. Microscopically, there were numerous scars in the heart muscle and an occasional Aschoff body was found. According to the pathologist, there were no changes in the heart which could be ascribed to radiotherapy.

Comment. The difficulties of making a just appraisal of the therapeutic value of irradiation of the cardiac area are obvious. Rheumatic heart disease, untreated, runs a variable course, sometimes with long remissions. In children, 85% with active carditis have a recurrence within 3 years.[5] Juvenile rheumatism shows a great tendency to relapse, with progressive damage to the tissues of the heart. In adults, the onset of myocardial insufficiency usually indicates that the termination of life is not far off; on the average,

death occurs within 3 years, during which the patient is partly or wholly incapacitated.[1]

In those instances recorded as improved, there appeared to exist a relationship between treatment and result. Lowering of temperature, fall in heart rate, lessening of the sedimentation rate of the erythrocytes and, above all, general clinical improvement, served as guides. The relief of cardiac pain in some cases was striking. To those who choose to say that these effects might have occurred in the absence of irradiation, we can present no final proof. Our experience has convinced us that the method is useful in selected cases.

Certain special features deserve comment. In a number of patients, in bed for months with signs of smouldering rheumatic activity, evidence of the subsidence of carditis has appeared soon after Roentgen therapy was begun. Several, in spite of severely damaged and greatly enlarged hearts, have remained free from demonstrable active carditis for over 10 years, although they have suffered from occasional respiratory infections and have, at times, had rheumatic twinges in the joints. One woman with early mitral disease when first seen, has worked for 10 years as an occupational therapist without increase in signs or recurrence of symptoms. Another woman, now 28 years of age, recently went through a normal pregnancy 9½ years after irradiation therapy; there has never been a return of rheumatic activity. A woman of 37 with agonizing abdominal pain due, it was believed, to rheumatic aortitis of the abdominal aorta, received 16 treatments over the abdomen during a period of 1 year. She has been free from discomfort for almost 6 years. A private patient followed by one of us, a woman, aged 37, had been in bed, running a low grade fever for 8 months. The heart was moderately enlarged; the signs were those of mitral stenosis, without congestive failure. Tonsillectomy had been performed without benefit. During a period of 6 months she received 8 irradiations. After the first treatment, the temperature fell to normal. Signs of mitral stenosis, of course, persist. But for 5 years she has led a normal life, running her household and participating actively in social activities. There has been no recurrence of carditis.

On the basis of a small material, generalizations are not justified. But it is our impression that the low grade infections respond better to irradiation than the more acute types; and that patients with congestive heart failure are poor subjects for this form of therapy. Early cases, with minimal cardiac damage, obviously offer the best chance for inducing a favorable response. On the other hand, a large heart with good functional capacity, appears to react well. Of the patients with cardiac pain, those with aortic insufficiency have obtained no relief, whereas those without this valvular defect have been uniformly helped. This is readily understandable. In aortic regurgitation with a large leak, the coronary flow is diminished and discomfort is due largely to relative ischemia of the myo-

cardium. When pain is due to rheumatic lesions in the heart muscle, an altered reaction of the cardiac tissues may aid in bringing about their dispersion.

Summary. 1. Forty-eight patients with rheumatic heart disease have been treated by Roentgen irradiation of the heart and have been observed during the past 11½ years.

2. In a considerable number the evidence indicated that radiation therapy exerted a favorable effect upon the lesions in the heart and upon the course of the disease. Those receiving the larger number of treatments, as a general rule, fared best.

3. Irradiation relieved cardiac pain in patients who did not have aortic insufficiency.

4. No harmful effects were noted. Unpleasant radiation reactions appeared in about half the cases.

5. Cases with low grade activity and without signs of congestive heart failure appear to be most benefited.

6. The manner in which improvement is initiated is not known. It is believed to be due to an altered response of the cardiac tissues induced by the rays.

7. Roentgen irradiation of the heart, in the present state of knowledge concerning rheumatic fever, deserves a place as a therapeutic measure in properly selected cases of active carditis.

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CLINICAL OBSERVATIONS ON THE DYNAMICS OF VENTRICULAR SYSTOLE.

IV. PULSUS ALTERNANS.*

BY LOUIS N. KATZ, M.D.,

DIRECTOR OF CARDIOVASCULAR RESEARCH, MICHAEL REESE HOSPITAL; ASSISTANT PROFESSOR OF PHYSIOLOGY, UNIVERSITY OF CHICAGO, CHICAGO, ILL.,

AND

HAROLD S. FEIL, M.D.,

ASSISTANT CLINICAL PROFESSOR OF MEDICINE, WESTERN RESERVE UNIVERSITY; ASSOCIATE PHYSICIAN, LAKESIDE HOSPITAL, CLEVELAND, OHIO.

(From the Cardiovascular Department, Michael Reese Hospital, and the Department of Medicine, Lakeside Hospital, Western Reserve University.)

ALTHOUGH pulsus alternans is a well known sign clinically and the subject of voluminous experimental and clinical investigation, the cause of the alternate large and small beats is still the subject of controversy. The field has been extensively reviewed by Poumail-

* Based on a study made on 5 patients taken from the medical wards of the City and Mt. Sinai Hospitals of Cleveland, Ohio.

loux[9] and by Kisch.[7] Since its first recognition by Traube,[11] it has been encountered in a variety of conditions, and when persistent, it has been regarded as a sign of grave prognosis. It may be a temporary condition in intoxications, in rapidly beating hearts such as paroxysmal tachycardia and in disturbances of rhythm, such as premature systoles. It may be a more or less permanent pulse phenomenon in myocardial degeneration, especially when associated with hypertension. It is then often associated with intraventricular block and gallop rhythm.

The definiteness of the clinical facts form a sharp contrast to the confusion regarding the causation of the phenomenon. The confusion has arisen in part because there is an apparent contradiction between the law of "all or none" response of the heart and the alternate size of the heart's response. The theories concerning the mechanism of pulsus alternans are numerous, but they can be grouped as shadings of two major concepts:

A. During systole some of the muscle fibers of the ventricles fail to contract because a prolonged refractory state in certain regions leads to localized blocks. One group of investigators maintains that this dropping out of muscle groups is confined to the small beats (Gaskell[2] and Hering[4]), while another group maintains that some muscle groups fail to contract in every systole, the number failing in the small beats being greater than in the large ones (Mines[8]).

B. Initiation and perpetuation of alternation is due in whole or in part to alternating dynamic changes of the heart set off by fluctuations in the circulation which are occurring constantly. The exact cause and effect relationship is not agreed upon by the exponents of this view (Wenckebach,[12] Frederique,[1] Straub,[10] Kahn[5] and Wiggers[13b]).

In view of this situation, it seemed to us that there was a need of careful study of the influence of alternation on the dynamics of ventricular systole in man utilizing the more accurate optical registration methods.[6] The present report is based on observations made on 5 patients with pulsus alternans. Changes in the duration of the phases of systole and diastole can be measured in man and in this way would be of help in correlating the experimental observations of Kahn,[5] Straub[10] and Wiggers[13b] with the clinical observations of Wenckebach.[12] Wiggers, for example, found that in experimental pulsus alternans the duration of systole in the large beats was noticeably longer than that of the small beats, and this was true also of the duration of the ejection phase. The isometric contraction phase, however, varied in just the reverse direction, and what is more important, so did the duration of diastole.

Case Reports. CASE 1.—J. M. (C. C. H.), a white male, aged 22, presented the picture of renal insufficiency associated with chronic glomerular nephritis. During his stay in the hospital, he developed pulsus alternans that

persisted until death. Records were taken on February 16, 1922, when his blood pressure was slightly elevated. The electrocardiogram showed normal sinus rhythm without any conduction disturbance (Fig. 1). The three heart sounds alternate slightly concordantly with the pulse; it is also to be noted that the small beats rise from a higher level than do the large beats —the higher level signifying a relatively greater arterial distention and a relatively greater diastolic blood pressure.

Shortly after this record was taken, exitus occurred, and the postmortem examination revealed beside the usual pathologic picture of chronic glomerular nephritis a moderately enlarged heart without valvular defect.

Table 1 was constructed from the measurements of 19 consecutive beats in two plates. The duration of each preceding diastole will be seen in Column II. The duration of this phase is variable but bears no definite relation to the height of the succeeding beats (Compare Columns I and II). Total systole varied little from beat to beat, although total systole due to the myocardial failure was shorter than the normal at corresponding rates.

TABLE 1.—CASE 1. ANALYSIS OF 17 BEATS.

I. Height of beat subclavian art. pulse mm.	II. Duration of previous diastole sec.	III. Duration of total systole sec.	IV. Duration of isometric contraction period sec.	V. Duration of ejection phase sec.	VI. Pulse gradient mm./sec.
		PLATE 1*			
26	....	0.215	0.041	0.174	149
19	0.310	.212	.051	.161	117
22	.310	.217	.040	.177	142
19	.313	.215	.050	.163	116
26	.316	.209	.038	.171	152
18	.316	.212	.050	.162	111
27	.318	.230	.045	.185	146
18	.306	.221	.061	.160	112
29	.323	.211	.034	.177	108
		PLATE 2*			
17	....	0.204	0.060	0.144	118
30	0.315	.201	.052	.149	201
19	.318	.192	.055	.137	138
31	.322	.199	.047	.152	204
22	.314	.197	.053	.144	152
28	.316	.191	.037	.154	182
19	.329	.194	.056	.138	135
30	.317	.190	.033	.157	190

* Heart rate 113 per min.

The isometric contraction period shows a striking alternation in its duration. Without exception this phase is longer in the smaller beats than in the larger beats. The difference between the duration of the isometric phase in successive beats ranged from 0.003 to 0.027 sec. The ejection phase also shows alternation, but the longer periods occur in the larger beats. Measurements of this phase in successive beats show a difference of 0.005 to 0.025 sec. The relative heights of the beats are given in Column I. The pulse gradient determined as described in a previous report[6] is greater in the larger beats.

CASE 2.—B. B. (C. C. H. No. 416), a negro male, aged 44, had congestive heart failure secondary to chronic hypertension (B.P. 194/180/130 on 6-29–22), with Cheyne-Stokes respiration. The patient was under observation for 2 years, during which period he persistently showed pulsus alternans of varying degree. Records were taken on several occasions. The electro-

cardiograms showed a definite prolongation of the *P–R* interval (Fig. 2). Alternation of the heart sounds also occurred, the first and second sounds being more intense in the large beats. The third heart sound, which by its position is attributed to auricular systole, is more intense in the cycle preceding the small beat (Fig. 2). In Table 2 are tabulated the measurements of 21 consecutive beats obtained from records on three different occasions. Previous diastole shows no definite alternation except on one occasion (9–26–22) where the longer diastoles precede the large beats. The variations in the durations of this phase are so slight as to be inconsequential. Total systole, which is shorter than the normal at corresponding rates, shows no consistent alternation. The isometric period was mostly prolonged in the smaller beats (0.002–0.018 sec.). Ejection, on the other hand, is abbreviated in the smaller beats.

TABLE 2.—CASE 2. ANALYSIS OF 21 BEATS.

I. Height of beat subclavian art. pulse mm.	II. Duration of previous diastole sec.	III. Duration of total systole sec.	IV. Duration of isometric contraction period sec.	V. Duration of ejection phase sec.	VI. Pulse gradient mm/sec.
			5/23/22*		
8	....	0.184	0.060	0.124	64
12	0.335	.195	.069	.126	95
8	.331	.195	.062	.133	60
12	.339	.196	.059	.137	87
9	.330	.197	.072	.125	72
12	.337	.200	.066	.133	89
9	.331	.199	.067	.132	68
11	.343	.190	.053	.137	80
9	.342	.191	.071	.120	75
			5/26/22†		
10	0.412	0.230	0.048	0.182	55
9	.395	.263	.076	.187	48
10	.437	.242	.052	.190	52
10	.453	.240	.054	.186	54
12	.453	.247	.053	.194	62
10	.456	.237	.049	.188	53
			9/26/22†		
15	....	0.218	0.079	0.139	107
17	0.460	.210	.069	.141	120
14	.452	.213	.070	.143	98
18	.465	.217	.068	.139	139
16	.457	.211	.071	.140	114
18	.460	.217	.065	.152	118

* Heart rate 110. † Heart rate 84.

CASE 3.—J. Wa. (C. C. H. No. 76525), a negro male, aged 55, was observed for several years during successive attacks of cardiac failure due to preëxisting vascular hypertension. Pulsus alternans was repeatedly observed but of varying degree. Records taken on May 17, 1922 (B.P. 130/110), of which Figure 3 is an example, show an alternation of the second heart sound associated with the alternating pulse, the second heart sound of the large beats being the more intense and longer in duration. Electrocardiograms show a prolonged *P–R* interval (Fig. 3). The measurements of 13 successive beats are tabulated in Table 3 in a manner similar to the preceding tables. Study of this table shows no constant relation between diastolic length and the size of the succeeding beat (Columns I and II); total systole shows no constant alternation (Column III), but the isometric

period is prolonged, the ejection shortened and the pulse gradient decreased in the smaller beats.

TABLE 3.—CASE 3. ANALYSIS OF 13 BEATS.

I. Height of beat subclavian art. pulse mm.	II. Duration of previous diastole sec.	III. Duration of total systole sec.	IV. Duration of isometric contraction period sec.	V. Duration of ejection phase sec.	VI. Pulse gradient mm/sec.
		PLATE 1*			
10	0.422	0.197	0.058	0.139	72
7	.418	.203	.068	.135	51
10	.416	.199	.059	.140	71
8	.420	.193	.062	.131	61
9	.425	.189	.065	.124	72
7	.413	.208	.071	.137	50
		PLATE 2*			
13	....	0.199	0.065	0.134	97
9	0.417	.190	.071	.119	76
12	.417	.207	.065	.142	83
10	.422	.190	.065	.125	80
12	.422	.199	.063	.136	88
9	.427	.192	.075	.117	77
111	.439	.189	.069	.120	92

* Heart rate 97.

TABLE 4.—CASE 4. ANALYSIS OF 14 BEATS.

I. Height of beat subclavian art. pulse mm.	II. Duration of previous diastole sec.	III. Duration of total systole sec.	IV. Duration of isometric contraction period sec.	V. Duration of ejection phase sec.	VI. Pulse gradient mm/sec
		PLATE 1*			
25	....	0.215	0.050	0.164	152
21	0.374	.209	.070	.139	151
29	.404	.196	.031	.165	182
20	.377	.204	.071	.133	150
30	.402	.196	.049	.147	204
23	.389	.201	.072	.129	178
29	.390	.216	.052	.164	176
		PLATE 2*			
24	....	0.214	0.074	0.140	171
37	0.411	.193	.052	.141	262
23	.394	.192	.084	.108	213
39	.405	.199	.054	.145	269
25	.377	.218	.078	.140	178
38	.409	.196	.046	.150	253
25	.371	.210	.073	.137	183

* Heart rate 100.

CASE 4.—J. Wi. (C. C. H. No. 76834), a negro male, aged 52, likewise suffered from congestive cardiac failure consequent to vascular hypertension (B.P. 220/140). During his failure, he developed Cheyne-Stokes breathing, and during his last admission, he developed pulsus alternans. The electrocardiograms showed that complete block coexisted with an unusually fast ventricular rate (100 per min.). The auricular rate was 150 (Fig. 4). Postmortem examination showed a considerably hypertrophied heart and a hemorrhage in the main stem of the bundle of His. From Table 4 it will be seen that the larger beats are preceded by slightly longer

diastoles, and the changes in systole and its phases are in accord with those of the preceding table. Associated with the alternating pulse is a concordant alternation of the second heart sounds (Fig. 4).

TABLE 5.—CASE 5. ANALYSIS OF 34 BEATS.

I. Height of beat subclavian art. pulse mm.	II. Duration of previous diastole sec.	III. Duration of total systole sec.	IV. Duration of isometric contraction period sec.	V. Duration of ejection phase sec.	VI. Pulse gradient mm/sec.
		PLATE 1*			
9	....	0.217	0.081	0.136	66
17	0.386	.237	.066	.171	99
7	P.S. .104	.201	.051	.150	47
33	.619	.225	.052	.173	191
1	.428	.227	.154	.073	14
19	.354	.247	.081	.165	109
7	.379	.219	.097	.122	57
16	.373	.205	.057	.148	108
10	.398	.203	.068	.135	74
		PLATE 2*			
11	....	0.276	0.129	0.147	74
18	0.317	.276	.116	.160	112
11	.324	.261	.113	.148	74
21	.363	.279	.119	.160	131
13	.296	.310	.156	.154	84
17	.300	.291	.131	.160	106
14	.331	.287	.130	.157	89
2	P.S. .208	.241	.149	.092	21
34	.505	.254	.077	.177	192
		PLATE 3*			
23	....	0.262	0.092	0.170	135
9	0.339	.302	.152	.150	60
15	.296	.261	.104	.157	95
12	.325	.329	.169	.151	79
16	.278	.289	.130	.159	100
12	.327	.299	.145	.154	78
15	.294	.284	.119	.165	91
5	P.S. .066	.234	.104	.130	38
36	.608	.206	.037	.169	213
		PLATE 4*			
12	....	0.281	0.155	0.126	95
8	0.336	.287	.170	.117	68
10	.342	.270	.145	.125	80
8	.345	.260	.112	.148	54
13	.356	.258	.099	.159	82
1	P.S. .055	.261	.207	.054	19
25	.652	.224	.054	.170	147

* Heart rate 100.
P.S. = Premature systole.

CASE 5.—J. Pol. (Mt. S. H. No. D. 1504), a white female, aged 50, had signs of early cardiac failure associated with vascular hypertension (B.P. 220/194/140). Pulsus alternans and premature ventricular beats were present. The alternation was most noticeable during heart failure. Electrocardiograms taken on April 7, 1924, showed the common type of bundle branch block unassociated with a prolongation in the *P–R* interval (Fig. 5). The concordant alternation of the second heart sound is also shown in

Figure 5. In Table 5 a slight alternation is seen at times in the duration of previous diastole (Column II), the taller beats succeeding shorter diastoles. There is an inconstant alternation of total systole, the shorter systoles occurring in the large beats. The alternation of the isometric period, ejection phase and pulse gradient are in keeping with the findings in the previous 4 patients.

Discussion of Results. The 5 cases of pulsus alternans detailed above consistently show associated with the alternation of the pulse, alternation in the intensity of the heart sounds, in the duration of the isometric and ejection phases and in the pulse gradient. The duration of total systole and of previous diastole showed no consistent alternation. While diastole occasionally alternated in duration, the changes were so slight as have little effect on ventricular filling. If diastole does exert an influence on filling, then this influence must be due to alternating changes in the duration of the isometric relaxation, rapid inflow or auricular systolic phases. In the present series we did not measure the duration of the diastolic phases which should be the subject of further clinical investigation.

The concordant alternation of heart sounds, especially the second sound, was a striking phenomenon in this series. The second sound was less intense in all cases and shorter in duration in 1 case (Case 3) in the smaller beats. A third heart sound was recorded in 2 cases. In one (Case 1) it occurred as a normal third heart sound during the rapid inflow phase. In the other (Case 2) it was evidence of augmented auricular activity accompanied by prolongation of the P–R interval. In both instances there was alternation of the third sound, it being more intense in the diastoles preceding the small beat.

This alternation of the sounds substantiates in man the observations of Wiggers made on animals[13a] that the intensity of the sound varies with the height of the intravascular tension.

The alternation of the isometric and ejection phases was discordant—in the small beats the isometric phase was relatively prolonged, while ejection was relatively shortened. In the large beats the reverse occurred; *i. e.*, the isometric phase was shortened and ejection prolonged. The fact that these phases altered in opposite directions explains the relative constancy of the duration of total systole.

The pulse gradient alternated concordantly with the size of the pulse, being less rapid in the smaller beats than in the large ones.

No alternation in the electrocardiograms was recorded in our series, although conduction changes were present in 4 cases (compare this with the reverse situation reported by Hamburger, Katz and Saphir[3]).

Interpretation of Results. Our results do not exclude the possibility that changes in refractory phase leading to alternating localized block may be the underlying mechanism of pulsus alternans. In

fact, the diverse forms of cardiac alternans and its varying manifestations can best be unified on such a basis.[3] In simplest terms, pulsus alternans would represent various forms of localized 2:1 intraventricular (intraäuricular or *A–V*) block. Such a condition, when operating in the left ventricle, could give rise to the dynamic changes described in the literature and the changes found by us in amplitude and slope of the pulse and in the duration of the systolic phases. On the other hand, our results do suggest that these dynamic changes could help to maintain the condition once it is initiated.

There is no doubt from past clinical experience and animal experimentation that pulsus alternans at slow heart rates indicates a badly damaged heart, and even in tachycardias this is true to a certain extent. In fact, it is probably safe to say that the seriousness of the permanent (as contrasted with the transient) damage to the heart varies: *a*, inversely with the rate of the heart; *b*, directly with the ease with which premature systoles, respiratory effort and marked sinus arrhythmia set it off; and, *c*, directly with the duration of its persistence following such precipitating factors.

In analyzing the possible rôle of dynamic changes in maintaining pulsus alternans, it is beside the point to argue that such dynamic changes can be brought about by 2:1 localized intraventricular block. It is much better, we believe, to see what the dynamic changes are and to examine whether or not they could lead to a perpetuation of the alternans *per se*.

From our results it is evident that alternation in the duration and force of ventricular systoles is not the result of alternation in the duration of diastole. In fact, Case 5 shows large beats following shorter diastoles and small beats after the longer diastoles. This is different from the experimental observations of Wiggers[13b] who found alternating changes in diastole. The possibilities exist, however: *a*, that the phases of diastole are changed alternately to permit more filling time before the large beat and less filling time in the small beat as postulated by Straub;[10] *b*, that the gradient of filling even with the filling time constantly alternates; and, *c*, that the auricular contribution itself may alternate and so make the total ventricular filling alternate also. Alternations in total filling need not be invoked, however, to explain differences in initial volume and tension of the left ventricle, since it stands to reason that the systolic residue will alternate, being greater after the small beat than the large. This is the view which Wenckebach[12] upheld. The work of Wiggers and Katz[14] has shown that such changes in initial volume and tension determine the character of the beat that follows, and our studies have shown that this also applies in man.[6] These experimental and clinical studies indicate that of all the variables initial volume and tension have the greatest influence on the dynamics of systole.

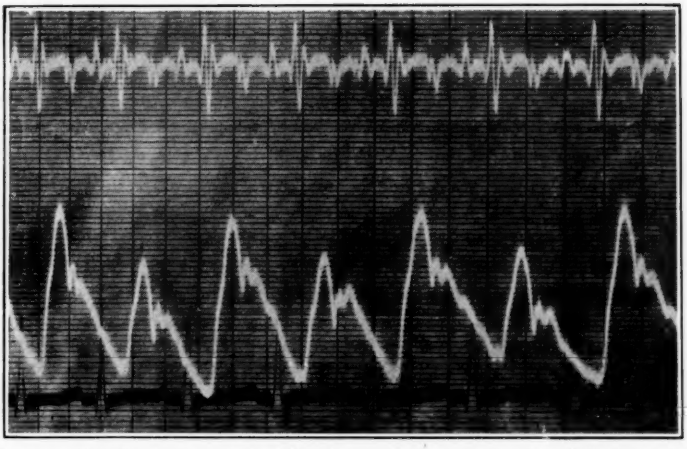

FIG. 1.—Simultaneous record of heart sounds (upper curve), subclavian arterial pulse (middle curve), and electrocardiogram, Lead II (bottom curve) in a patient with pulsus alternans (Case 1). I, 1st heart sound; II, 2d heart sound; III, 3d heart sound. Time in this and subsequent figures in fifths of a second.

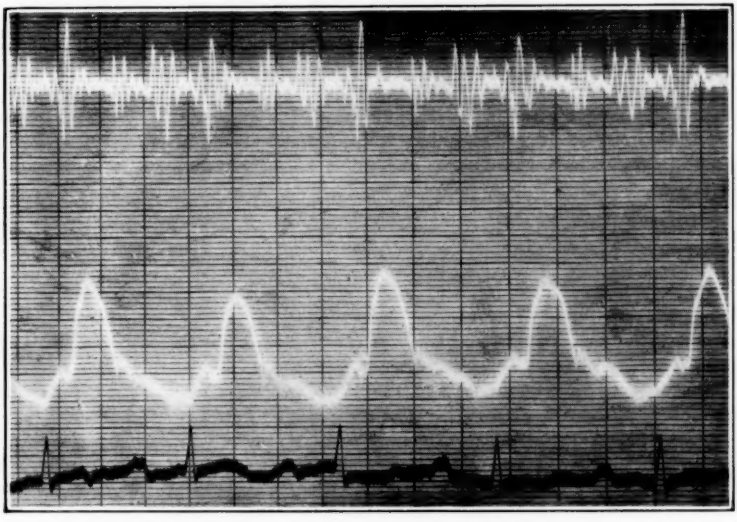

FIG. 2.—Record of Case 2. Items as in Figure 1.

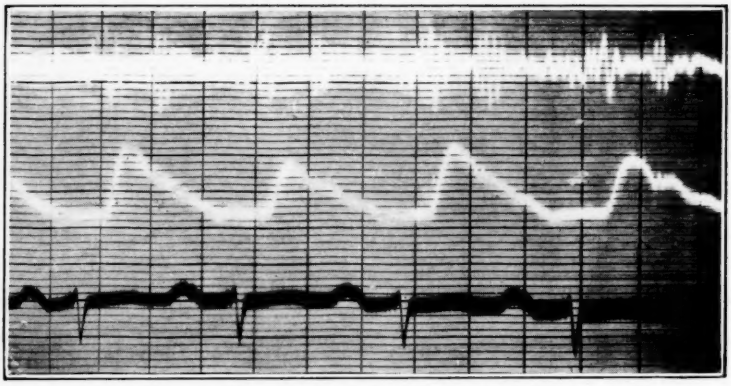

FIG. 3.—Record of Case 3. Items as in Figure 1.

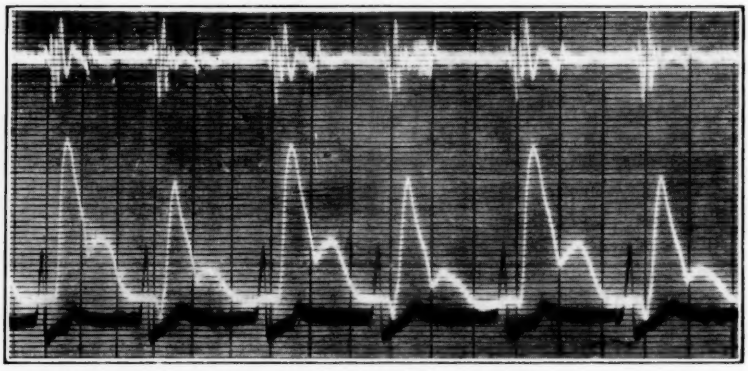

FIG. 4.—Record of Case 4. Items as in Figure 1. No 3d heart sound.

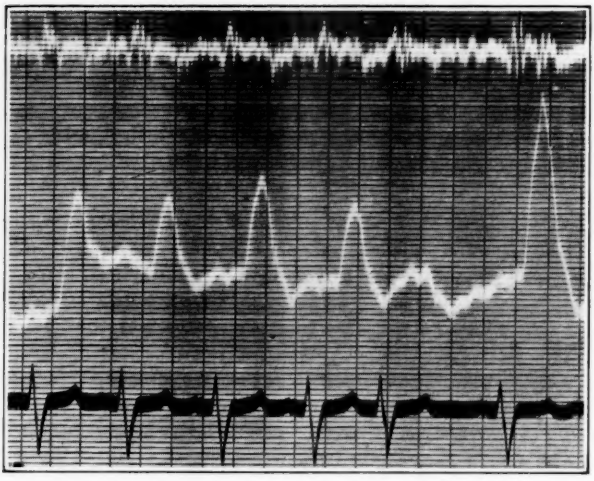

FIG. 5.—Record of Case 5. Items as in Figure 1. No 3d heart sound.

Assuming the above to be true, let us follow the changes in dynamics from beat to beat. Starting with a small beat, whatever its cause, with its reduced ejection rate and shortened ejection time we may conclude that the amount of blood ejected is reduced; consequently, there is an increased systolic remainder. This results in an increased initial volume and tension which explains the dynamics of the next beat, its magnitude, its rate of contraction and the duration of its systolic phases. Because the residue is large, the systole of the damaged heart empties it beyond the normal, and consequently, the residue for the succeeding beat is decreased beyond the normal and a small beat follows. This cycle of events continues for a variable time. Another factor which probably helps to accentuate this alternation is the change in diastolic pressure (the resistance to emptying), which is less in the diastole preceding the large pulse than in the one preceding the small pulse. Diastolic pressure therefore tends to hinder the emptying of the small pulse, permits a greater emptying of the large pulse and thereby tends to perpetuate the overswinging of the systolic remainder. This cycle of events may continue more or less indefinitely. The importance of initial tension and volume is further supported by the evidence given in Case 4 where large beats followed an effective auricular contraction, and small beats followed diastoles without auricular contributions.

Alternation may be initiated with a large pulse following an extrasystole, since the latter dynamically has the same effect as the small pulse of an alternans. A sudden change in rhythm may likewise initiate alternations in the initial tension and diastolic volume of the ventricle. This phenomenon may be started by marked variations in the depth of breathing such as occur in dyspnea and Cheyne-Stokes breathing. These also operate dynamically in the same manner as outlined above. There are thus several possible circulatory changes present in all cases which can initiate alternation in initial tension and volume.

We wish to make it clear that we have not proved that dynamic changes of one beat alone produce the dynamic changes in the next beat and so perpetuate pulsus alternans, nor have we proved that circulatory changes initiate pulsus alternans mechanically. The evidence we present, however, strongly suggests that such dynamic factors may help to initiate and perpetuate pulsus alternans.

Summary. The dynamics of systole in 5 clinical cases of pulsus alternans were studied by optical registration methods. The following conclusions were reached:

1. The alternation in the size of the pulse is accompanied by concordant alternations in the heart sounds, the gradient of the pulse and the duration of ejection, and by a discordant alternation in the duration of the isometric period. The duration of total systole showed no alternation.

2. No alternations were found in the electrocardiograms in this series, although conduction disturbances were present in 4 of the cases.

3. The duration of diastole did not vary consistently and was so small as to be without significance in explaining the alternation of the pulse volume.

4. In the case with complete heart block the pulsus alternans is attributed to contribution of auricular stimuli in alternate diastoles.

5. The evidence presented in this report, when correlated with previous studies of the dynamics of systole, supports the view that changes in initial volume and tension such as follow extrasystoles, sudden changes in rhythm and in respiration (so often present in alternation) can help to initiate the phenomenon of pulsus alternans. Once established alternate variations in systolic residue occur which alternately increase and decrease the initial tension and volume and so help to perpetuate the phenomenon. It is not denied that changes in the refractory phase are important in initiating and perpetuating pulsus alternans, but it is emphasized that the changes in initial tension and volume are likewise important.

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SUPPURATIVE PLEURITIS COMPLICATING PULMONARY INFARCTION IN CONGESTIVE HEART FAILURE.

By Israel Steinberg, M.D.,

ASSISTANT VISITING PHYSICIAN, BELLEVUE HOSPITAL; INSTRUCTOR IN MEDICINE, NEW YORK UNIVERSITY COLLEGE OF MEDICINE,

Eugene Clark, M.D.,

ASSISTANT PATHOLOGIST, BELLEVUE HOSPITAL; INSTRUCTOR IN PATHOLOGY, NEW YORK UNIVERSITY COLLEGE OF MEDICINE,

AND

Clarence E. de la Chapelle, M.D.,

VISITING PHYSICIAN, BELLEVUE HOSPITAL; ASSISTANT PROFESSOR OF MEDICINE, NEW YORK UNIVERSITY COLLEGE OF MEDICINE, NEW YORK CITY.

(From the Third (New York University) Medical Division of Bellevue Hospital, the Department of Medicine of the New York University College of Medicine, and the Department of Pathology, Bellevue Hospital.)

Although it is widely recognized that pulmonary infarction accompanied by a serous effusion frequently occurs in congestive heart failure, it appears to be less well known that sterile pulmonary

embolism and thrombosis may be followed by infection and suppuration of the hemorrhagic infarct with pleural extension and suppurative pleuritis.[1,3–6] We are of the opinion that this occurs not uncommonly, for we have encountered 4 instances of this complication at necropsy in Bellevue Hospital during the past 3 years. Clinically, it is not always possible to decide whether infection of the infarct is spontaneous and of bronchiogenic origin, or whether it is attributable to contamination of the pleural space during thoracentesis performed for the initially clear and sterile effusion of pulmonary infarction, which usually precedes the suppurative pleuritis.

We are reporting the following cases from the Third Medical and Psychiatric Divisions of Bellevue Hospital, because they present morphologic evidence that the suppurative process in the pleura follows infection and suppuration of the infarcts with extension to the pleural space.

Case Reports. CASE 1.—T. H., a 47-year-old expressman, was admitted on January 19, 1934, for dyspnea and pain in the left chest. Eight weeks earlier he had experienced a sudden, severe substernal pain, which was followed by increasing dyspnea, cough productive of rusty streaked sputum and orthopnea. Three weeks before admission a severe sharp pain appeared in the left axilla.

Physical examination revealed an acutely and chronically ill white male, dyspneic, orthopneic, cyanotic. There were signs of fluid at the left base. The apical impulse was not palpable, a gallop was audible, the rate 120, the blood pressure 108/90. There were no palpable abdominal viscera, no edema or clubbing of the extremities.

The temperature was 102° F., the white blood count 22,850 with 89% granulocytes. The Wassermann reaction was negative, the blood culture sterile, and the sputum negative for tubercle bacilli.

The following day 2 liters of serosanguinous fluid were removed from the left chest. Dyspnea was diminished but signs of consolidation persisted in the axilla. The pleural fluid was sterile on culture; it contained many neutrophils and red blood cells but no organisms were visible on microscopic examination. On January 23 another thoracentesis of the left chest yielded 240 cc. of similar serosanguinous fluid. Pitting edema of the ankles, a palpable liver and icterus were soon noted. The initial and all subsequent electrocardiograms showed sinus tachycardia and left bundle branch block.

On January 28 symptoms and signs of a pulmonary infarct in the right lower chest appeared (Fig. 1). On February 8 the signs of sudden embolic closure of the left brachial artery were noted, but these soon subsided without gangrene. Evidence of fluid at the right base indicated thoracentesis on February 23, which yielded 500 cc. of serosanguinous fluid, sterile on culture. This was repeated on February 27 and fluid of identical character was obtained. On March 8 another tap of the right chest was performed and 175 cc. of thick foul pus were obtained, which on culture yielded many diphtheroids and a few isolated streptococcus hemolyticus colonies. The patient appeared prostrated with a persistently high fever and leukocytosis. Surgical drainage was thought inadvisable because of his poor general condition. Death occurred on March 16, 1935.

At necropsy (few hours after death), both lungs were found expanded and bound by dense fibrous adhesions to the parietal pleura. The pleura over the right lung measured almost a centimeter in thickness. Thick yellowish purulent fluid was encapsulated at both bases. Six wedge-shaped

infarcts were found in the left lung and a similar number in the right. The central portions of most of the infarcts appeared necrotic.

Microscopic sections of the infarcts revealed areas of hemorrhagic infarction in various stages of resolution, necrosis, organization and suppuration. In several sections the infarcted zones appeared as necrotic amorphous debris surrounded by zones of dense neutrophilic infiltration and organization. The arteries were plugged by recent and organizing thrombi and the pleural membrane was thickened by an organizing purulent exudate. Numerous rods and a few isolated cocci were demonstrated within the necrotic infarcts, as well as in the pleural exudate, in the Gram-Weigert sections.

The final anatomic diagnosis was: Chronic bilateral suppurative pleuritis with encapsulated empyema, multiple pulmonary infarcts with necrosis and suppurative pneumonitis, multiple pulmonary arterial thrombosis and embolization, hypertrophy and dilatation of the heart, coronary atherosclerosis, organized thrombus of the right coronary and anterior descending branch of the left coronary artery, old myocardial infarcts, mural thrombosis of the right and left ventricles and the right auricular appendage, arteriolar nephrosclerosis, old infarct of the left kidney, chronic passive congestion of the liver.

Summary of Case 1. A 47-year-old arteriosclerotic cardiac suffered myocardial infarcts which were accompanied by mural thrombi in both ventricles and in the right auricular appendage. Evidence of multiple pulmonary infarcts with pleural effusion appeared, and thoracentesis yielded a sterile serosanguinous fluid which was followed, after repeated taps, by the appearance of foul pus containing diphtheroids and hemolytic streptococci. Necrosis, infection and suppuration of the pulmonary infarcts were demonstrable at necropsy.

Case 2.—J. A., a 45-year-old male, was admitted to the hospital on November 21, 1934. It was learned that he was admitted to another hospital on February 26, 1934, because of precordial pain, of 12 days' duration, which radiated to the left shoulder and arm. Clinical and electrocardiographic evidence of coronary occlusion and myocardial infarction were found. A Roentgen plate taken soon after entry into that institution, showed a patch of consolidation at the left base which was interpreted as a pulmonary infarct. He improved and was discharged on April 11, 1934, but reëntered the same institution in May 17, 1934, because of the recurrence of precordial pain, cough, weakness and dyspnea. He remained on their wards in congestive heart failure, until November 21, 1934 when he became mentally disturbed and was transferred to Bellevue Hospital.

On examination, he appeared dyspneic, orthopneic, and cyanotic. There were râles at both bases and signs of a left pleural effusion. The heart sounds were distant, the blood pressure 100/90. On November 26 blood tinged expectoration was noted, and physical and roentgenologic signs of consolidation in the right upper lobe, with pleuritis and fluid at the right base, were obtained. The temperature rose to 102° F., the white blood count to 19,400 with 96% granulocytes. Thoracentesis of the right chest yielded 75 cc. of serosanguinous fluid. Some air was put in after the tap to secure better visualization of the lung field, and the Roentgen ray plate showed breaking down of the area of consolidation in the right upper lobe, and a fluid level at the base (Fig. 2). Death occurred the following day, December 4, 1934.

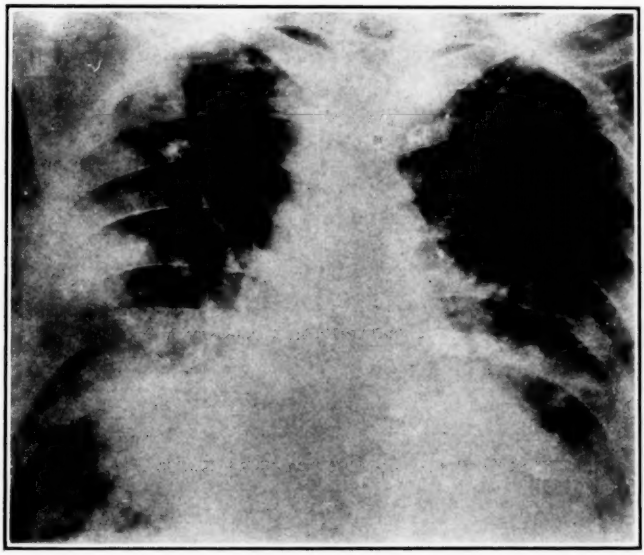

FIG. 1.—Multiple areas of density, particularly at the base of the right lung. There is enlargement of the heart.

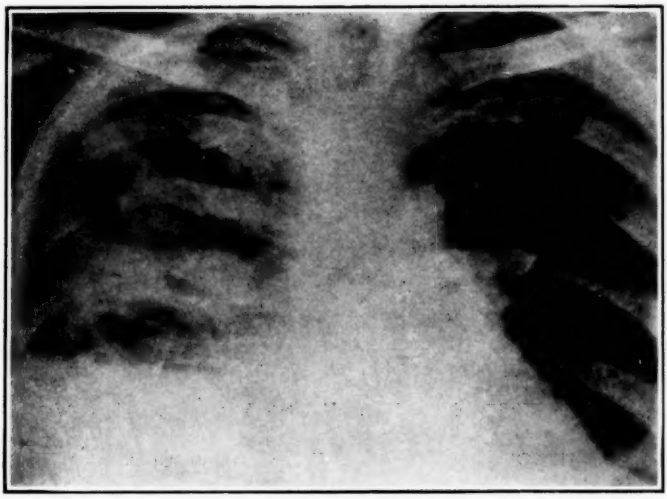

FIG. 2.—Multiple areas of excavation in the right upper lung field. A fluid level is visible at the right base (air was introduced for better contrast study).

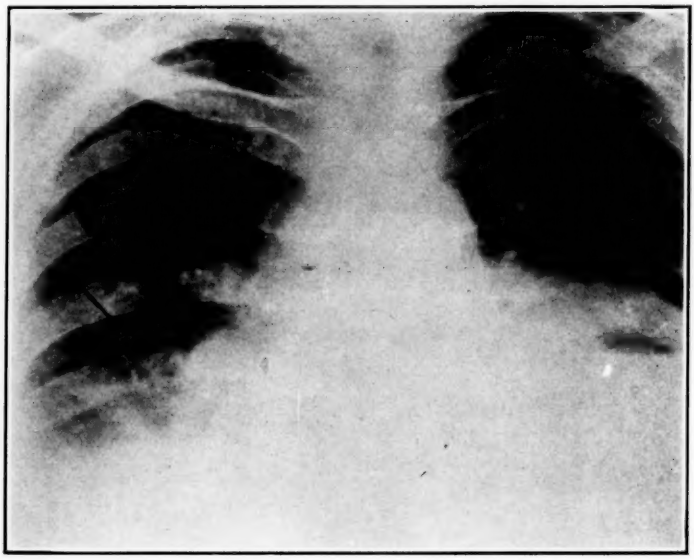

FIG. 3.—Changes of chronic passive congestion and a fluid level on the left (air was introduced for contrast after the tap). A patch of density is visible above the fluid level.

At necropsy, performed 6 days after death, the left pleural cavity contained about 225 cc. of clear serous fluid. In the lower half of the right pleural sac was an encapsulated cavity, lined by a thick purulent membrane and filled with thick purulent material. A large area in the posterior aspect of the right upper lobe appeared necrotic, and within it was a cavity about 6 cm. in diameter, limited from the pleural space by a thin shell of friable lung tissue. The pleural surface of the wall of the cavity showed a fibrinous membrane which extended downward to become continuous with the pyogenic membrane over the right lower lobe. The major branches of the pulmonary artery to the right upper lobe were plugged with organizing thrombi which extended to the edge of the necrotic area.

Microscopic sections through the right upper lobe showed the cavity to be lined by necrotic infarcted lung. In some areas the outlines of the necrotic alveolar walls were still discernible and the alveolar spaces were filled with hemolyzed red cells and pigmented macrophages. Elsewhere the wall consisted of amorphous necrotic débris. Surrounding the necrotic wall there was dense infiltration by polymorphonuclear leukocytes with abscess formation. A narrow rim of young granulation tissue and organizing pneumonitis limited the lesion from the uninvolved lung. The arteries were plugged by organized and canalized thrombi, and the pleural surface was covered by a membrane of fibrin and numerous neutrophils. Large bacterial clumps, containing cocci and bacilli, were found within the areas of necrosis and suppuration and in the pleural membrane. Similar bacterial clumps were seen in the mural thrombus in the right ventricle, but since there was no sign of inflammation of the underlying wall, it was believed that this represented agonal or postmortem bacterial invasion and proliferation.

The final anatomic diagnosis was: Acute encapsulated fibrinopurulent pleuritis, pulmonary infarction of right upper lobe with necrosis, cavitation, and suppurative pneumonitis, pulmonary arterial embolism and thrombosis, hypertrophy and dilatation of the heart, atherosclerosis of the coronary arteries and organized thrombosis of the anterior descending branch of the left coronary artery, organized infarct of the anterior left ventricular wall, organizing mural thrombi of the right and left ventricles, chronic passive congestion of the liver, arteriolar nephrosclerosis.

Summary of Case 2. A 45-year-old arteriosclerotic cardiac suffered a coronary thrombosis accompanied by a myocardial infarct and mural thrombosis of both ventricles. Several episodes suggesting pulmonary infarction were observed, and the last of these was followed by extensive necrosis, cavitation and suppuration of the infarct, with pleural extension and encapsulated suppurative pleuritis.

CASE 3.—G. B., a 49-year-old male, first came under our observation on October 18, 1933, at which time he entered the hospital because of cough and blood-streaked expectoration. He acquired a chancre in 1926, and had experienced dyspnea and radiating precordial pain on exertion since 1929. These symptoms had become more marked in the 2 weeks preceding admission, and a bloody expectoration appeared. Physical examination revealed signs of enlargement of the heart and aortic insufficiency. There were no signs of congestive heart failure. There were auscultatory and Roentgen-ray signs of pulmonary consolidation corresponding to the right middle lobe, and later a friction rub appeared. There was fever for 3 days, the sputum showed unclassified pneumococci and the blood culture was negative. The pulmonary signs cleared and convalescence was interrupted

by two brief severe attacks of precordial pain. He was discharged on November 3, 1933. The Wassermann reaction was negative.

He reëntered on February 20, 1935, for the consideration of hemorrhoidectomy. Signs of congestive heart failure were now clearly evident and he was transferred to the medical service without operation. On March 5th pain in the right chest, bloody expectoration and grunting respirations appeared. There were dulness, diminished breath sounds and râles at both bases, and a friction rub was audible in the right axilla. The temperature fluctuated between 102 and 105° and signs of fluid appeared at the right base. Thoracentesis, performed on March 13, yielded 50 cc. of thick greenish-yellow pus. Closed-tube drainage was instituted but exitus occurred the following day.

At necropsy (few hours after death) the right pleural cavity was filled with tenacious yellow-green pus which covered all surfaces, but was particularly thick over the dependent and diaphragmatic surfaces of the right lower lobe. In the right upper lobe was a small recent infarct. The dependent portions of the right lower lobe presented a firm, dry, dark-red appearance and within this hemorrhagic area were small irregular grayish-white zones. The arteries leading to the dependent portion of the right lower lobe were plugged by thrombi. The postmortem lung-culture yielded hemolytic streptococci and unclassified pneumococci.

Microscopic sections through the right lower lobe revealed a varying picture. There were well demarcated areas of hemorrhagic infarction partly surrounded by zones of neutrophilic alveolar exudation with necrosis of alveolar walls, abscess formation and extension to the pleura. Numerous cocci, appearing generally as paired or isolated organisms, less commonly in chains, were demonstrable in these regions in the Gram-Weigert preparations. Elsewhere were zones of acellular, eosinophilic, amorphous débris encircled by a region of suppurative pneumonitis.

The final anatomic diagnosis was: Acute fibrinopurulent pleuritis, right, hemorrhagic infarction and suppurative pneumonitis of right lower lobe, pulmonary arterial thrombosis or embolization, hypertrophy and dilatation of the heart, syphilitic aortitis with fusiform aneurysm of the ascending aorta, coronary ostial stenosis and aortic insufficiency, thrombosis of the right auricular appendage, chronic passive congestion of the liver.

Summary of Case 3. A 49-year-old white male, with syphilitic heart disease, aortic insufficiency and coronary ostial stenosis, developed signs of hemorrhagic infarction of the lung while in congestive heart failure. The initial thoracentesis, performed 8 days following the appearance of symptoms of pulmonary infarction, yielded frank pus. Necropsy revealed areas of suppurative pneumonitis surrounding the infarct and postmortem lung culture disclosed the presence of pneumococci and hemolytic streptococci.

Case 4.—J. M., a 41-year-old chronic alcoholic, who had been repeatedly admitted for acute alcoholism, entered the hospital on January 10, 1936, in a condition of acute alcoholic intoxication. The heart did not appear enlarged on physical examination, and the blood pressure was 150/108. There were no signs of congestive heart failure, but edema of the legs and neurologic evidence of peripheral neuritis were noted.

While ambulatory on the wards, on January 20, 1936, he suddenly exhibited paroxysmal dyspnea, orthopnea, cyanosis and evidence of congestive heart failure. The blood pressure was 110/90, a gallop was audible

at the apex, the rate was 130, and the standard and precordial lead electrocardiograms suggested myocardial infarction involving the anterior wall of the left ventricle.

On January 25, 1936, bloody expectoration appeared and signs of fluid at the right base, and consolidation at the left base, were elicited. Thoracentesis of the right chest on January 30 yielded 700 cc. of clear yellow fluid. Thoracentesis was repeated on the right, and also performed on the left chest, on February 11, and 175 cc. of turbid yellow fluid were obtained from the former, and 1400 cc. of turbid brownish fluid from the latter. The cells in the pleural fluid were mostly lymphocytes (88% and 78% respectively). Both chests were retapped on March 6 with similar results. The patient continued in a downhill course showing progressively severe failure. Physical and Roentgen-ray evidence (Fig. 3) of bilateral effusion persisted. On April 16 thoracentesis of the left chest yielded 700 cc. of grayish fluid; although neutrophils predominated in the smear of the sediment, no organisms were demonstrable by Gram staining. The right chest was retapped on April 17 and 300 cc. of bloody fluid obtained, and again tapped on April 21, at which time a similar fluid was obtained, yielding Streptococcus viridans on culture. The patient's condition grew rapidly worse and death occurred on May 17, 1936.

At necropsy (2 hours after death) about 500 cc. of purulent fluid were found in the right pleural sac, and about 850 cc. of similar fluid were encapsulated at the base of the left pleural cavity. The visceral and parietal pleura measured 5 mm. or more in thickness and consisted of dense fibrous tissue with a superficial layer of shaggy fibrinous material. Projecting into the encapsulated empyema cavity at the left base, was a large, well circumscribed infarct, which appeared as a friable, softened, necrotic, reddish-gray mass. A similar smaller infarct, with its base at the diaphragmatic pleura, was encountered in the anteromedial portion of the right lower lobe. The pulmonary arteries at the hilus of the left lung contained organizing thrombi, and more distally, the vessels were completely occluded by partially and completely organized thrombi. The large arteries in the right lower lobe were similarly occluded but the vessels were patent at the hilus.

Microscopic sections of the infarcts showed well demarcated zones of infarction from which most of the blood had already been resorbed, leaving necrotic remnants of alveolar walls. The peripheral rim of necrotic lung was densely infiltrated by neutrophils and abscesses were frequently encountered. A few isolated cocci were demonstrated in these regions by the Gram-Weigert technique. The infarcts were circumscribed from the uninvolved lung by a broad zone of granulation tissue, and the arteries were occluded by organized thrombi. The pleura was markedly thickened and covered by a layer of fibrin and neutrophils.

The final anatomic diagnosis was: Chronic bilateral fibrinopurulent pleuritis, multiple organizing and softened pulmonary infarcts with suppurative pneumonitis, multiple organizing pulmonary arterial thrombi or emboli, hypertrophy and dilatation of the heart, coronary atherosclerosis, patchy fibrosis of apex of the left ventricle with superimposed organizing mural intraventricular thrombi, chronic passive congestion of the liver, multiple infarcts of the kidneys, ascites.

Summary of Case 4. A 41-year-old chronic alcoholic, with an enlarged heart and coronary atherosclerosis, suddenly developed signs of myocardial infarction and congestive heart failure. This was followed by signs and symptoms of pulmonary infarction at both bases, accompanied by an initially serous effusion. Thoracentesis

was repeatedly necessary, and the pleural fluid assumed a purulent character almost 3 months following the pulmonary infarction. Streptococcus viridans was obtained on culture of the chest fluid on one occasion. Necropsy revealed old necrotic infarcts surrounded by zones of suppurative pneumonitis and undergoing organization.

Discussion. The gross and microscopic findings in all 4 cases support the view that secondary infection of the pulmonary infarcts led to suppurative pneumonitis and pleuritis. In 2 cases (2 and 3) the possibility of contamination of the pleural space by thoracentesis may be excluded. In Case 3 the initial tap was purulent, and in Case 2, although the initial tap was sero-sanguinous, necropsy performed the following day disclosed a purulent effusion, which had evaded thoracentesis because of encapsulation at the base, in addition to the serosanguinous effusion. The suppuration of the infarcts and of the lung immediately surrounding the latter, in all 4 cases, further fortifies the belief that the pleura became infected by microörganisms invading from the lung and not introduced during thoracentesis.

The emboli and thrombi responsible for the infarcts were of bland character, and the former were derived from mural thrombi in the right auricular appendage and ventricle in Case 1, in the right ventricle in Case 2, and in the right auricular appendage in Case 3. The source of the emboli was not demonstrated in Case 4, but the peripheral venous system was not examined.

The microörganisms which caused the pulmonary and pleural suppuration varied in type. *Strep.* hemolyticus and diphtheroid bacilli were cultured from the pleural fluid in Case 1, *Strep.* viridans from the pleural fluid in Case 4, and hemolytic streptococcus and pneumococcus were demonstrated by postmortem culture of the lung in Case 3. The abundance of the bacterial colonies in the sections of the lung and pleura in Case 2, and their presence in the mural thrombus of the right ventricle, are probably attributable to postmortem bacterial proliferation and invasion, occurring in the 6-day interval between death and necropsy.

The source of the microörganisms and their route of dissemination to the pulmonary infarcts have not been ascertained. It is probable that the bacteria were derived from the respiratory passages. Ceelen[1] has expressed the belief that bronchogenic dissemination of microörganisms may bring about suppuration of a pulmonary infarct. Holman and Mathes[2] have experimentally produced abscess formation in bland pulmonary infarcts by intravenous injections of microörganisms. In the cases herein reported, however, bronchogenic infection appears the more likely route. Blood cultures taken in 2 of the 4 cases (1 and 3) were sterile. Bronchogenic infection of the lungs is a common occurrence in congestive heart failure and frequently brings about secondary pneumonia. It is

probable that the infarcted lung offers an unusually favorable soil for the propagation of bacteria, and that in the presence of ischemic necrosis, extensive suppuration rapidly ensues. In only one subject (Case 3) did the suppurative pneumonitis complicate recent pulmonary infarction, and in this instance the initial tap yielded purulent fluid. In the other cases the infarcts were older, and had undergone softening (Cases 1 and 4), and cavitation (Case 2), and the clinical signs suggest that the infarcts antedated the suppurative pleuritis by a period varying from several weeks (Case 2), to 2 and 3 months (Cases 1 and 4). In the interval between infarction and empyema sterile pleural effusions were encountered.

Clinical experience with these cases reflects the confusion in differential diagnosis which may arise when the cardiac nature of the initial symptoms is unrecognized or inadequately correlated with the subsequent pulmonary phenomena. The latter may simulate pulmonary neoplasm, pneumococcus or streptococcus pneumonia with postpneumonic empyema, or cavernous pulmonary tuberculosis with pleural effusion.

Although empyema was recognized clinically in 3 of the cases, the coexistence of severe congestive heart failure discouraged surgical interference. That such cases may be occasionally amenable to surgical drainage is illustrated by Touroff's[6] experience, in which recovery followed thoracotomy for infrapulmonary empyema associated with pulmonary infarction in a rheumatic cardiac with congestive heart failure.*

Summary. In the foregoing report are presented the clinical and necropsy findings of 4 cases of congestive heart failure, in whom suppurative pleuritis complicated pulmonary infarction. The evidence is discussed which indicates that bland pulmonary infarcts may spontaneously undergo secondary infection which leads to empyema by penetration of the microörganisms to the pleura.

* Recently, one of us (C. C.) had the privilege of observing and treating a case of suppurative pleuritis following pulmonary infarction secondary to coronary thrombosis, at the Lenox Hill Hospital. Surgical drainage was performed by Dr. Carl Eggers and the patient made an uneventful recovery. However, several months later he returned to the hospital in congestive heart failure. Bed rest and digitalis partially restored his cardiac reserve.

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OBSERVATIONS ON THE ETIOLOGIC RELATIONSHIP OF ACHYLIA GASTRICA TO PERNICIOUS ANEMIA.

VI. THE SITE OF THE INTERACTION OF FOOD (EXTRINSIC) AND GASTRIC (INTRINSIC) FACTORS; FAILURE OF *in Vitro* INCUBATION TO PRODUCE A THERMOSTABLE HEMATOPOIETIC PRINCIPLE.*

BY W. B. CASTLE, M.D.,

ASSOCIATE PROFESSOR OF MEDICINE, HARVARD MEDICAL SCHOOL; ASSOCIATE DIRECTOR, THORNDIKE MEMORIAL LABORATORY,

CLARK W. HEATH, M.D.,

INSTRUCTOR IN MEDICINE, HARVARD MEDICAL SCHOOL; ASSISTANT PHYSICIAN, THORNDIKE MEMORIAL LABORATORY,

MAURICE B. STRAUSS, M.D.,

INSTRUCTOR IN MEDICINE, HARVARD MEDICAL SCHOOL; JUNIOR VISITING PHYSICIAN, BOSTON CITY HOSPITAL,

AND

ROBERT W. HEINLE, M.D.,

RESEARCH FELLOW IN MEDICINE, HARVARD MEDICAL SCHOOL; RESEARCH FELLOW, THORNDIKE MEMORIAL LABORATORY; ASSISTANT IN MEDICINE, BOSTON CITY HOSPITAL, BOSTON, MASS.

(From the Thorndike Memorial Laboratory, Second and Fourth Medical Services (Harvard), Boston City Hospital, and the Department of Medicine, Harvard Medical School.)

IT is well known that the oral or parenteral administration of suitable extracts of mammalian liver leads to increased blood production and clinical improvement in patients with pernicious anemia. The oral administration of normal human gastric juice (intrinsic factor) together with beef muscle[2,3,4a] or certain other substances[1,12] (extrinsic factor) produces identical effects in such patients. The livers of persons who have died of pernicious anemia before treatment could be applied are lacking in the active principle present in normal human and animal livers.[11] These facts have led to the assumption that the effective principle in the liver of the normal person is in some way formed from the interaction of food and gastric factors. The problem as to how and where in the body such a transformation occurs remains, however, quite unsolved.

Convincing evidence is lacking for any specific enzyme action of normal human gastric juice *in vitro* on the nitrogenous components of sources of extrinsic factor.[6–8] Indeed, it has been shown that normal human gastric juice freed by adsorption methods of both pepsin and rennin still contains intrinsic factor.[4b,9] Klein and Wilkinson's[10] claim that they have demonstrated the *in vitro* synthesis of the active principle of liver in incubated mixtures of preparations of hog's gastric mucosa and beef muscle cannot be accepted,

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because the mixtures were not subjected to the relatively high temperatures, 80° to 120° C., known to be without significant destructive effect on relatively crude liver fractions. The fact that the administration of beef muscle and gastric juice *separately* at an interval of 6 hours results in increased blood production[2] eliminates the necessity of hypothecating an *in vitro* phase for the production of the activity of incubated mixtures. Although the respective administration of beef muscle and gastric juice separated by an interval of 12 hours or more leads to negative effects on blood production,[2] this fact in no way defines the site of effective interaction between beef muscle and gastric juice when given coincidentally. Indeed, the fact that neutral mixtures of beef muscle and gastric juice are effective when administered to the achylic pernicious anemia patient implies that a neutral reaction is suitable for the development of their activity. Therefore, so far as the reaction is concerned a suitable environment might be found as well after absorption within the body as before leaving the alimentary tract.

Obviously, more information concerning the site and the conditions essential for interaction of the extrinsic and intrinsic factors is desirable. The purpose of this communication, therefore, is to present evidence that an essential stage in the development of a hematopoietic principle takes place, possibly *in vitro*, but certainly within the alimentary tract rather than parenterally. The active principle of liver, however, is not formed *in vitro* by the interaction of food and gastric factors. The conditions of the observations suggest that if an enzyme is involved in the interaction between extrinsic and intrinsic factors, it is not active in an environment more acid than pH 2.5.

Methods. The 9 patients on whom the present observations were made all had typical Addisonian pernicious anemia and responded eventually and characteristically to the administration of mixtures of beef muscle and gastric juice or to the administration of liver extract. The methods of dietary control and of red blood cell and reticulocyte counting, as well as the interpretation of effects on blood production, have been fully described elsewhere.[3,4a] The gastric juice was secreted daily by normal fasting individuals following the intramuscular injection of 0.5 mg. of histamine. It was kept in the ice box without neutralization until required for use. After incubation the semi-liquid mixture of beef muscle and gastric juice was given daily to the patient by stomach tube.

Observations. *Mixtures of beef muscle and gastric juice administered at pH 1.8 to 2.5 are ineffective.* The purpose of the following observations was to determine whether a change in the reaction of the upper alimentary tract would affect the blood-forming activity of mixtures of beef muscle and gastric juice. To effect this, use was made of the natural buffering properties of incubated mixtures of beef muscle and gastric juice. By means of a stomach tube either acid or neutral mixtures were administered.

The contents of the stomach of a normal man was recovered 1

hour after the ingestion of a meal of 300 gm. of beef muscle. It was then liquefied by subsequent incubation at 37.5° C. at pH 2.5—half of it for 6, and half of it for 30 hours. To Case 2 this material was given daily at pH 2.5 during a first period. No significant effect on blood production appeared, as is shown in the table. In the immediately following second period, the procedure was identical *except that the incubated gastric contents was brought to pH 5* with a saturated solution of sodium hydroxide immediately before administration to the patient. A positive effect on blood production appeared. To Case 71 was given daily during a first period a mixture of 200 gm. of beef muscle, 150 cc. of gastric juice and 5 gm. of pepsin, incubated for 6 hours at pH 1.8 and administered at that reaction. No significant effect on blood production appeared. In the immediately succeeding second period, the daily procedure was the same *except that the material was brought to pH 7* by the addition of a saturated solution of sodium hydroxide immediately before administration to the patient. A positive effect on blood production appeared, as is shown in the table.

Whether the failure of the acid digest to cause increased blood production was due to the destruction of the extrinsic or the intrinsic factors before effective interaction could occur or whether it was due to such acidity that interaction could not take place was the basis of further analysis. That the administration of such an acid digest of beef muscle may influence for some time the reaction of the upper intestinal contents is probable, since concentrated sodium hydroxide equivalent to 450 cc. of 0.1 normal sodium hydroxide solution was required in order to bring the mixture from pH 1.8 to neutrality. Therefore, although incubation of a mixture of beef muscle and gastric juice at pH 1.8 or 2.5 for 6 hours did not abolish its activity provided it was brought to pH 5 or 7 before being given to the patient, if the mixture was not so neutralized it could be argued that after administration to the patient continued *in vivo* incubation of the acid mixture was responsible for failure through subsequent destruction of the intrinsic factor.[2] In order to test this possibility, 200 gm. of beef muscle were incubated with 5 gm. of pepsin and 150 cc. of gastric juice for 12 hours at pH 1.8. This material was then brought to pH 7 and given to Case 72 daily. A significant effect on blood production resulted (Table 1). It therefore appears probable that the negative effect of administration of incubated mixtures of beef muscle and gastric juice at an acid reaction in Cases 2 and 71 was not due to a prolongation of any destructive action of the acid medium on the extrinsic or intrinsic factors after administration to the patient.

Therefore, unless in some way the acidity of the mixture merely prevented the absorption of one or more of the active constituents of the digests, it is reasonable to suppose that the administration of the mixture of beef muscle and gastric juice at an acid reaction

inhibited the essential interaction between these substances. The fact that a change in the pH of the mixture would not significantly affect the pH of the parenteral tissues certainly suggests that with neutral digests an interaction takes place, possibly *in vitro*, but at least within the alimentary tract rather than parenterally. That this interaction is carried out by an enzyme in the gastric juice is possible, though by absorption with Hammarsten casein solution we[4b] (see also second period of Case 78 in the table), as well as Helmer, Fouts and Zerfas,[9] have prepared filtrates of normal human gastric juice containing active intrinsic factor but apparently without pepsin or rennin-like action. Moreover, the *in vitro* observations of Griffiths[7] and of Helmer and Emerson[6,8] do not appear to have demonstrated a specific enzyme acting on sources of extrinsic factor. Nevertheless, if the specific effect on extrinsic factor is produced by an enzyme it can now be stated as probable that its activity occurs in the vicinity of the neutral point and is slight, if any, at reactions of pH 2.5 or less.

Temperatures without significant destructive effect on aqueous solutions of an unpurified liver extract abolish the activity of mixtures of beef muscle and gastric juice after incubation for 2 hours at pH 7. In the preparation of the liver fraction "G" of Cohn, Minot and their associates,[5] temperatures of 80° C. are employed. Moreover, the activity of neutral aqueous solutions of this fraction successfully resists boiling or autoclaving as a means of sterilization. Thus in the table are shown the positive effects on blood production in a patient with pernicious anemia, Case 73, who was given daily by intramuscular injection a neutral aqueous solution of liver fraction "G" which had previously been autoclaved for 3 hours at 120° C. The daily dose was 2 cc., containing material derived from 10 gm. of liver. It is thus clear that in order to establish the presence of such a thermostable substance in a mixture of beef muscle and gastric juice the activity of the mixture should withstand autoclaving and certainly lower temperatures.

The material given daily during the first period of Case 74 was prepared as follows. Two hundred grams of beef muscle, 5 gm. of pepsin and 100 cc. of water were incubated at 37.5° C. at pH 2.5 to 3.5 for 6 hours. Then 75 cc. of gastric juice were added and the mixture was incubated at 37.5° C. at pH 7 for 2 hours. Thereafter hydrochloric acid was added until a pH of 2.5 to 3.5 was attained and the mixture incubated for 72 hours at 40° C. The material so prepared in advance was finally adjusted to pH 5 and given daily with no significant effect on blood production. In an immediately succeeding second period the procedure was identical *except that the material was not incubated for 72 hours at 40° C.* A positive effect on blood production resulted.

Temperatures without significant destructive effect on aqueous solutions of liver extract abolish the activity of mixtures of beef muscle with

normal human duodenal contents or with hog duodenal and small intestinal mucosa after incubation for 2 hours at pH 7. Since the *in vitro* incubation of beef muscle and gastric juice was not shown to produce a substance resembling in thermostability the active principle of liver, the question arose as to whether such a substance would be formed if a further *in vitro* imitation of normal digestive processes was attempted by the addition of normal human duodenal contents or of hog duodenal and small intestinal mucosa.

Accordingly, during the first period of Case 75, the following procedure was carried out. One hundred grams of beef muscle, 4 gm. of pepsin and 50 cc. of water were incubated at 37.5° C. for 12 hours at pH 2.5 to 3.5. This liquid material was then introduced into the stomach of a normal fasting subject into whose duodenum had previously been passed a Levin catheter. To 200 cc. of the duodenal contents recovered, which contained bile and partially digested beef muscle, were added 200 gm. of beef muscle and 4 gm. of pepsin. The mixture was then incubated for 1 hour at pH 2.5 to 3.5. Then 125 cc. more of the duodenal contents were added and the mixture incubated at pH 7 for 2 hours. The material was then boiled for 5 minutes, cooled, and immediately given to the patient, Case 75, daily by stomach tube during a first period. No significant effect on blood production resulted. In an immediately subsequent second period, however, during which the procedure was the same *except that the final mixture was not boiled for 5 minutes*, a positive result appeared, as is shown in the table.

During the first period of Case 76, the following procedure was carried out daily. Two hundred grams of beef muscle, 100 cc. of water and 5 gm. of pepsin were incubated at 37.5° C. for 2 hours at pH 2.5 to 3.5. Seventy-five cubic centimeter of gastric juice were then added, the mixture was brought to pH 7 and incubated for 1 hour. Then 100 gm. of freshly prepared mucosa, stripped from the duodenum and upper small intestine of hogs, were added and the mixture was incubated for 1 hour at pH 7, then heated to from 70° to 80° C. for 30 minutes. Immediately after cooling, the material was given daily to Case 76 without significant effect on blood production, as is shown in the table. During an immediately succeeding period the same procedure was carried out daily *except that the final mixture was not heated to 70° to 80° C. for 30 minutes.* A positive result appeared (Table 1).

It is therefore evident that the incubation of the mixtures of beef muscle with normal human gastric juice and subsequently with normal human duodenal contents or with the mucosa of the duodenum and small intestine of the hog does not produce *in vitro* a substance which is resistant to heat, as is the active principle of whole liver or of relatively unpurified liver extract.

That the destructive effect of temperature on the mixture given these patients was not on the extrinsic factor in the beef muscle is

TABLE 1.—EFFECT OF ACIDITY OR OF VARIOUS TEMPERATURES ON THE HEMATOPOIETIC ACTIVITY IN PERNICIOUS ANEMIA OF INCUBATED MIXTURES

TABLE 1.—EFFECT OF ACIDITY OR OF VARIOUS TEMPERATURES ON THE HEMATOPOIETIC ACTIVITY IN PERNICIOUS ANEMIA OF INCUBATED MIXTURES OF BEEF MUSCLE WITH GASTRIC JUICE OR WITH VARIOUS INTESTINAL PREPARATIONS.

First Periods.—Daily Administration of Various Substances as Indicated Below.

Days of treatment.	CASE 2.		CASE 71.		CASE 72.		CASE 73.		CASE 74.		CASE 75.		CASE 76.		CASE 77.		CASE 78.	
	Gastric contents containing 200 gm. beef muscle incubated 6–30 hours at pH 2.5.		Beef muscle 200 gm., pepsin 5 gm. gastric juice 150 cc. incubated 6 hours at pH 1.8.		Beef muscle 200 gm., pepsin 5 gm. gastric juice 150 cc. incubated 12 hours at pH 1.8. Given at pH 7.		Solution liver extract — Lilly (N.N.R.), autoclaved 3 hours at 120° C. 2 cc. from 10 gm. of liver intramuscularly.		Beef muscle 200 gm., pepsin 5 gm., gastric juice 75 cc. incubated 2 hours at pH 7, then incubated for 72 hours at pH 2.5–3.5. Given at pH 5.		Beef muscle and duodenal contents incubated 2 hours at pH 7, then boiled 5 min. (See text for details.)		Beef muscle and hog duodenal and small intestinal mucosa incubated 2 hours at pH 7, then 70°–80° C. for 30 min. (See text for details.)		Beef muscle 200 gm., pepsin 5 gm. incubated 48 hours at pH 2.5–3.5, then boiled 5 min. Then added to gastric juice 75 cc. at pH 7.		Beef muscle 200 gm., pepsin 5 gm. digest added to gastric juice 75 cc. previously incubated at 40° C. for 72 hours at pH 1.5. Given at pH 5.	
	R.B.C. (mils.).	Retics. (%).	R.B.C. (mils.).	Retics. (%).	R.B.C. (mils.).	Retics. (%).	R.B.C. (mils.).	Retics. (%).	R.B.C. (mils.).	Retics. (%).	R.B.C. (mils.)	Retics. (%).	R.B.C. (mils.).	Retics. (%).	R.B.C. (mils.).	Retics. (%).	R.B.C. (mils.).	Retics. (%).
0	1.03	3.8	1.60	1.6	2.09	0.8	2.23	0.4	2.40	0.0	2.24	0.2	1.28	0.2	1.44	0.8	1.25	1.2
2	0.75	2.5	1.44	1.0	1.82	1.2	2.25	3.6	2.14	0.4	2.20	0.2	1.19	0.4	1.33	0.6	1.53	0.4
4	1.07	1.6	1.48	2.2	1.73	1.2	2.06	7.0	2.42	0.4	2.25	0.1	1.37	0.4	1.46	0.4	1.21	0.4
6	0.75	4.6	1.58	1.0	1.83	0.8	2.35	10.2	2.52	0.8	2.00	0.2	1.23	1.0	1.43	3.2	1.22	0.8
8	0.69	3.2	1.55	0.8	1.90	4.8	2.67	**16.2**	2.65	0.6	1.94	0.4	1.15	0.1	1.56	7.4	1.01	1.6
10	0.84	3.2			1.84	**11.6**	....	7.4	2.99	1.6					1.62	**11.6**		
12							....	....							....	6.0		
14							2.73	....										

Second Periods.—Daily Administration of Various Substances as Indicated Below.

	Same as above except given at pH 5.		Same as above except given at pH 7.				Same as above except *not* incubated 72 hours at pH 2.5–3.5.		Same as above except *not* boiled 5 min.		Same as above except *not* heated 70°–80° C. for 30 min.			Same as above except gastric juice filtrate used after iso-electric precipitation with casein, then shaken with basic magnesium carbonate.	
	R.B.C. (mils.).	Retics. (%).	R.B.C. (mils.).	Retics. (%)			R.B.C. (mils.).	Retics. (%).	R.B.C. (mils.).	Retics. (%).	R.B.C. (mils.).	Retics. (%).		R.B.C. (mils.).	Retics. (%).
2	0.65	3.4	1.30	0.4			2.87	0.2	1.82	0.2	1.04	0.1		1.09	1.0
4	0.80	9.8	1.15	2.4			2.77	3.2	2.10	3.8	0.85	0.1		1.28	1.6
6	0.86	6.6	1.37	1.1			2.92	2.6	1.85	2.6	0.93	7.2		1.22	3.2
8	0.89	**16.0**	1.36	1.8			2.85	6.8	1.92	**12.5**	1.16	**14.2**		1.35	8.4
10	1.10	15.0	1.39	5.0			3.09	**7.0**	2.21	5.4	1.28	8.0		1.42	**19.6**
12	1.44	7.4	1.50	**7.6**			....	2.6	2.56	0.8				1.86	12.4
14	1.48	5.1	1.57	2.6										1.97	2.8

clear. Mixtures of gastric juice with a 48-hour peptic digest of beef muscle previously boiled for 5 minutes (Case 77, Table 1), with autoclaved, autolyzed yeast (Vegex)[12] or with hog stomach mucosa which has been boiled for 2 hours,[2] are hematopoietically effective. It is, however, possible that the destructive effect of temperature on mixtures of beef muscle and gastric juice may have been due simply to destruction of the intrinsic factor. We have shown elsewhere that the activity of the intrinsic factor of gastric juice is significantly diminished by incubation at 37.5° C. for 2 hours at pH 1.5[2] and is completely destroyed by incubation at 40° C. for 72 hours at pH 1.5[4b] (first period of Case 78, Table 1), by a temperature of 70° to 80° C. for 30 minutes[2] or by boiling for 5 minutes.[1] Nevertheless, opportunity for the development of a thermostable substance from the already liquefied beef muscle during the 2-hour incubation at neutrality, especially in the presence of both normal gastric and duodenal contents, would appear to have been provided.

Klein and Wilkinson[10] claim to have demonstrated the *in vitro* synthesis of the active principle of liver in an incubated mixture of a preparation of hog stomach with beef muscle. They found that the activity in pernicious anemia of "haemopoietin," a preparation derived from hog stomach, was destroyed by exposure to a temperature of 60° to 65° C. for 30 minutes. After incubation with beef muscle at 37° C. for 2 or 6 hours at pH 5.7, however, the activity of the mixture was not destroyed by a temperature of 60° to 65° C. for 30 minutes. On the contrary, our observations in the first periods of Cases 74, 75 and 76 show that subsequent incubation at 37.5° C. for 72 hours, boiling for 5 minutes or heating to 70° to 80° C. for 30 minutes destroyed the blood-forming activity of beef muscle after 2-hour incubation at 37.5° C. at pH 7 with gastric juice, duodenal contents and small intestinal mucosa, as shown in the second periods. Since such temperatures are not destructive of the activity of dilute solutions of the fraction "G" of Cohn, Minot and their associates, it is clear that without other means of identification it cannot be assumed that this relatively thermostable substance was formed *in vitro*. Since Klein and Wilkinson did not test the destructive effect of temperatures above 60° to 65° C., their evidence that the thermostable active principle of liver extract was synthesized *in vitro* cannot be accepted. Indeed, the rather slight differences in thermostability observed may have been entirely due to the protective effect of the beef muscle on the preparation of hog stomach mucosa. It cannot be denied, however, that some new substance of slightly greater thermostability than the hog stomach preparation may have been synthesized in their experiments.

Conclusions. 1. Administration of mixtures of beef muscle and normal human gastric juice at pH 1.8 or 2.5 does not lead to the

increased blood production in pernicious anemia which occurs when mixtures of these substances are administered at pH 5 or pH 7.

2. Since the negative results from administration of such acid mixtures were shown not to be due to destruction of intrinsic factor, it is probable that the acid environment was unsuitable for an essential interaction between beef muscle and gastric juice.

3. Since the inhibitory effect of the acid environment would be largely confined to the alimentary tract, it is inferred that normally the essential interaction between extrinsic and intrinsic factors takes place enterally rather than parenterally.

4. The synthesis of a substance resembling in thermostability the active principle of crude liver extracts was, however, not effected *in vitro* by 2-hour incubation at pH 7 of beef muscle with (*a*) normal human gastric juice or (*b*) thereafter with normal human duodenal contents or (*c*) with normal human gastric juice and thereafter with hog duodenal and small intestinal mucosa.

5. Despite lack of present evidence for specific *in vitro* effects, the possibility remains that the gastric intrinsic factor is an enzyme active near pH 7, but not at pH values less than 2.5. If active under *in vitro* conditions, its function would appear to be the development of some precursor of the thermostable active principle of liver extract.

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THE ETIOLOGY AND TREATMENT OF IDIOPATHIC HYPOCHROMIC ANEMIA.*

By W. M. Fowler, M.D.,

ASSOCIATE PROFESSOR OF MEDICINE, UNIVERSITY OF IOWA MEDICAL SCHOOL,

AND

Adelaide P. Barer, Ph.D.,

RESEARCH ASSISTANT, UNIVERSITY OF IOWA MEDICAL SCHOOL,

IOWA CITY, IOWA.

(From the Department of Internal Medicine, State University of Iowa Medical School, Iowa City, Iowa.)

During iron balance experiments on patients with hypochromic anemia, certain observations were made regarding the pathogenesis of that form which is commonly known as "idiopathic hypochromic

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anemia." Though much has been written on this disease, and many hypotheses advanced to explain its etiology,[3,26] little in the way of absolute proof to support these assumptions has been forthcoming. The clinical and hematological features have been sufficiently emphasized so that a detailed discussion of these is unnecessary. In this anemia, occurring almost exclusively in middle-aged women usually associated with a deficient gastric secretion, the erythrocytes are small and pale. Dysphagia, koilonychia, paresthesia without evidence of cord degeneration, and glossitis are of frequent occurrence, together with the usual symptoms of a severe anemia. A history of excessive blood loss is seldom obtained, so that the actual etiology of the anemia has been in doubt.

There are many similarities between this anemia and that of chronic hemorrhage. Insofar as the blood smear is concerned, there is nothing in the morphological changes of the erythrocytes on which to base a differentiation of the two conditions, and there are no essential differences in the color, volume, or saturation indices. Koilonychia, which has been frequently emphasized as a feature of the idiopathic form, may be present in chronic hemorrhagic anemia as is evidenced by the following case:

Case Abstract. A white male, aged 47, began to have periodic epigastric distress 15 years before admission to this hospital. The distress appeared intermittently and there were several episodes of severe hemorrhage. A diagnosis of duodenal ulcer was made, and a gastro-enterostomy was performed. He felt quite well until 5 years prior to his admission when he had a hemorrhage so severe that he was confined to bed for several months. He had lost no gross blood since that time, but had continued to be weak and pale. These symptoms increased, and at the time of admission he presented the usual manifestations of severe anemia.

Chemical examination of the stools revealed that he continually passed small amount of occult blood. There were 1.5 gm. of hemoglobin per 100 cc. of blood, 1,100,000 erythrocytes per cm., and an hematocrit of 7%. The finger nails were thin, brittle, and spoon shaped, and the patient had noted the onset of these features 2 years previously. Under medical management, the bleeding became less severe but did not entirely cease. With the administration of iron and ammonium citrates, 3 gm. per day, the hemoglobin increased to 9.2 gm., and the erythrocyte count to 4,910,000, and the finger nails became normal.

Although dysphagia, glossitis, and atrophy of the tongue are frequent in idiopathic hypochromic anemia, we have never encountered these features in a case of chronic hemorrhagic anemia unassociated with deficient gastric secretion. These manifestations, together with the achlorhydria, are the only characteristics that suffice for differentiation of the two conditions aside from the history of chronic hemorrhage. Dysphagia was present in 6 of the 11 cases of idiopathic hypochromic anemia on whom iron balance determinations were made, and in every instance it disappeared completely when the blood hemoglobin returned to normal with no dilatation of the esophagus except that incident to a single esophagos-

copy. We do not believe, however, that the anemia *per se* is responsible for the esophageal spasm inasmuch as it did not occur in any of the cases with uncomplicated chronic hemorrhagic anemia.

Menstrual Blood Loss. The fact that idiopathic hypochromic anemia is almost exclusively confined to women, and especially to women of the child bearing age, has naturally led to the assumption that the periodic menstrual blood loss is one factor in its etiology. On the other hand, menorrhagia has been considered by some to be a result or a symptom of the anemia rather than the cause. We have questioned our patients carefully in regard to their menstrual blood loss and none was included in the idiopathic group who acknowledged excessive menstruation. All those with such a history were classified as chronic hemorrhagic anemia, regardless of the gastric acidity or other findings.

During the iron balance studies,[10,11,12] it was necessary to ascertain the amount of iron and hemoglobin lost during menstruation in several instances, but in attempting to evaluate these results a review of the literature gave us no definite information as to what constituted the normal menstrual blood loss. We, therefore, made such determinations in 100 non-anemic, normal women, who, as far as they could judge, had a normal menstrual flow. It was found[1a] that the hemoglobin lost per menstrual period varied from 0.68 gm. to 23.57 gm. which represented from 6.6 to 178.7 cc. of the patient's blood. The average loss for the 100 subjects was 50.6 cc. of blood, and 50% of the women lost between 23 and 68 cc. In general, there was some correlation between the amount of hemoglobin lost, the duration of the menstrual flow, and the number of napkins used; but in certain instances there was a marked discrepancy. It is obvious that one cannot depend entirely on the patient's statement as to the normality of the menstrual flow, as she has no standard on which to base a comparison. When these menstrual losses were considered in terms of iron, it was found that a daily iron retention of from 0.08 mg. to 3.29 mg. would be necessary to replace that lost through menstruation alone. Although none of these women were anemic, it is apparent that even a supposedly normal menstrual flow may constitute a serious drain on the iron stores of the body, and undoubtedly will lead to an anemia when associated with certain other abnormalities.

The menstrual blood loss was determined in 11 cases of idiopathic hypochromic anemia and in every case the individual had considered this loss to be normal. It will be noted (Table 1) that the hemoglobin lost per period varied from 3.18 gm. to 54.36 gm., and that in only 3 cases was the loss within the average range for the 100 normal women. The daily iron retention necessary to counteract the menstrual iron loss varied from 0.38 mg. to 6.5 mg. The results of our iron balance determinations convince us that these higher figures cannot be supplied from the dietary iron alone, since a daily iron

retention of this amount was seldom encountered. The last column in Table 1 gives the actual iron balance for 10 of these patients with idiopathic hypochromic anemia while they were receiving a diet with an iron content of from 10 to 13 mg. per day. It will be noted that in only 2 cases (Cases 2 and 6) was the iron retention sufficient to replace that lost through menstruation. The reason for the development of anemia in these patients is evident from these figures.

Achlorhydria. The frequency with which idiopathic hypochromic anemia is associated with a deficient gastric secretion, as manifest by achlorhydria or hypochlorhydria, has naturally led to the assumption that this feature is either the cause or a prominent contributing factor to the anemia through its influence on the absorption of iron

TABLE 1.—RELATIONSHIP OF MENSTRUAL LOSS TO IRON RETENTION.

Case.	Age.	Blood Hb., gm.	Blood hematocrit, %.	RBC, mills.	Menstrual loss.			Daily iron retention necessary to replace menstrual loss, mg.	Actual daily iron balance with normal diet, mg.
					Iron, mg.	Hb., gm.	Blood, cc.		
1 . .	34	4.91	27.5	4.91	10.64	3.18	49.20	0.38	−1.37
2 . .	28	6.55	31.0	4.85	10.70	3.19	48.70	0.38	+1.67
3 . .	38	12.41	43.0	5.44	12.24	3.65	29.41	0.43	−7.12
4 . .	34	6.14	31.0	4.48	20.57	7.14	116.28	0.73	+0.20
5 . .	40	6.20	29.0	3.63	47.38	14.14	228.06	1.69	
6 . .	37	6.46	34.0	4.77	49.59	14.80	229.12	1.77	+2.91
7 . .	44	6.26	28.0	4.07	53.42	15.94	254.31	1.91	+0.14
8 . .	25	10.90	36.0	4.52	59.73	17.82	163.48	2.13	−2.62
9 . .	35	4.72	20.5	3.88	145.89	43.54	922.45	5.21	−3.39
10 . .	41	11.80	26.0	4.33	163.00	48.65	412.29	5.82	+1.24
11 . .	40	12.01	38.0	4.75	182.07	54.36	452.42	6.50	−6.66

from the gastro-intestinal tract. Achlorhydria has been demonstrated in patients several years before the development of the anemia,[17] and a hypochromic anemia has also been observed as a sequel to gastrectomy.[13] Wintrobe[26] reports that 17% of the females, and 12.6% of the males had achlorhydria as determined from 11,000 gastric analyses in adults of all ages and Van der Hoof and Davis,[23] in 240 cases of uncomplicated anacidity, found that 69 were males and 171 were females. Only 3 of these males were anemic, whereas 99 of the females had a hemoglobin below 80%. Although it is recognized that iron is better absorbed from an acid than from an alkaline medium, this factor alone does not explain the great preponderance of the disease in females. Further discussions on the relationship of achlorhydria are given by Witts,[27] Faber and Grim,[9] Waugh,[24] and by Wintrobe.[26]

Additional proof that achlorhydria interferes with the absorption of iron is furnished by our iron balance studies. It was found that with a normal iron intake obtained from food alone, the absence of free hydrochloric acid in the gastric juice led to a diminished iron

absorption.[1c] In 11 cases with achlorhydria, 8 (72.8%) were in a negative iron balance, and the average daily iron balance for the entire group showed a loss of 4.38 mg. In 15 cases with a normal or low gastric acidity only 5 (33⅓%) were in a negative iron balance, and the average daily iron retention for the group was 1.02 mg. These results show, both by the average daily iron balance, and by the percentage of cases in negative iron balance, that the disturbed gastric secretion diminished the absorption of iron from a normal diet. It was shown, however, that the administration of dilute hydrochloric acid did not increase iron absorption either with a normal dietary iron intake or when large amounts of iron were being administered. This feature suggests that it may not be the lack of hydrochloric acid itself that is at fault but that there may be a deficiency of some unrecognized substance.

These results substantiate the belief that a deficient gastric secretion interferes with the absorption of iron, and that this is an important etiological factor in the production of anemia. Since it does not explain the sex and age incidence of the disease, it is obvious that other factors play a part. When combined with the iron loss in menstruation, the explanation for the anemia as well as the lack of spontaneous improvement becomes evident.

Diet. A dietary deficiency has been suggested as the etiologic factor in many cases of idiopathic hypochromic anemia, especially a diet so low in its iron content that the requirements of the body are not fulfilled. Farrar and Goldhammer[10] found the iron requirement of the body to be considerably below the usually accepted values[7] and although their patients received from 4.9 to 9.1 mg. of iron per day over long periods of time, they were in positive iron balance and did not develop anemia. Ohlson and Daum[19] found the requirements to be much higher. Our results in 5 patients on a daily iron intake of from 4.14 to 6.74 mg. showed all to be in negative iron balance, but when 4 of these subsequently received from 12.27 to 14.19 mg. of iron per day they were then in a positive balance.[1c] These results indicate that the requirements are above the figure given by Farrar and Goldhammer, and more nearly agree with Ohlson and Daum. We have never encountered a case of severe idiopathic hypochromic anemia in which we felt that the diet was sufficiently low in its iron content so that this in itself would account for the anemia. We believe that the achlorhydria is of more importance than the actual restriction of the iron intake in the majority of cases.

Pregnancy. It has been noted that the onset of idiopathic hypochromic anemia is frequently associated with pregnancy and in many instances there have been repeated pregnancies with a noticeable weakness persisting between the periods of gestation. Most of these patients with hypochromic anemia of pregnancy have achlorhydria[20] and glossitis and this type of anemia has been considered as identical to the idiopathic form. Wintrobe[26] found that in 17%

of his patients with idiopathic hypochromic anemia, the onset was quite definitely related to pregnancy. The onset of the anemia in 2 of the 11 patients on whom balance studies were done seemed to be related to frequent and repeated pregnancies.

A diet deficient in iron has been noted in many of the reported cases of hypochromic anemia of pregnancy.[22] It has been assumed that the fetal demand for iron so depletes the maternal stores that anemia develops, and Coons[6] has brought forward more definite proof to substantiate this assumption. She has demonstrated a higher storage of iron in the early months of pregnancy than during the latter part, and has shown that the retention during the late months falls short of the calculated fetal requirements. She has also shown that only the best diets can supply the demands of the maternal organism in the latter months of gestation so that a diet deficient in iron is more apt to be of significance in this type of anemia than in the idiopathic form. The similarity of this anemia to the idiopathic form, and the apparent transition of one to another, certainly point to their being the same disease. In one, the iron is lost through menstruation, in the other, through fetal requirements, and in both there is a deficient absorption of iron because of achlorhydria.

Iron Metabolism. It has been assumed that faulty metabolism of iron, aside from improper absorption, may be a causative factor in some cases of idiopathic hypochromic anemia. We have found no concrete evidence in the literature to support this hypothesis, and in our own studies have accumulated some evidence against it. Comparing the retention of iron in cases of idiopathic hypochromic anemia and of chronic hemorrhagic anemia receiving the same amount of iron and ammonium citrates, it was found that there was no essential difference; in fact, the idiopathic cases retained a slightly higher percentage of the administered iron than did the others.[11] As was pointed out, however, the highest retention in the cases with hemorrhage was so close to that of the lowest retention in the idiopathic cases that the difference in the averages of the two groups is probably of no consequence. There was no significant disparity in the rapidity of hemoglobin formation nor in the percentage of the iron used in hemoglobin formation. In Table 2 are shown the percentage of iron retained, the percentage utilized in hemoglobin formation, and the daily hemoglobin increase in each of 3 cases of idiopathic and of chronic hemorrhagic anemia. These results were obtained in cases which were studied[11] over a sufficiently long time for the hemoglobin regeneration to be of significance. Since there was no difference in the iron retention nor in the utilization of this iron in the formation of hemoglobin, there can be no significant alteration in the metabolic processes related to iron utilization.

Treatment. The treatment of idiopathic hypochromic anemia consists in the administration of adequate amounts of iron in a

suitable form.[21] It does not differ from the treatment of chronic hemorrhagic anemia, nor the hypochromic anemia of pregnancy except for the fact that a less rapid hemoglobin response may occur in cases with achlorhydria. Strauss[21] has given the following dosages for the commonly used iron preparations: Reduced iron 3 gm., ferrous carbonate 4 gm., iron and ammonium citrates 6 gm., and ferrous sulphate 1 gm. Iron and ammonium citrates have also been recommended in dosages as high as 9 gm. per day. Minot and Heath[18] have presented a standard for the expected reticulocyte response with iron administration, and Heath[14] has emphasized the factors which must be controlled in any accurate clinical investigation of the results of iron therapy. He regards a rise of 0.16 gm.

TABLE 2.—IRON RETENTION AND UTILIZATION. IRON INTAKE, 500 MG. DAILY

Case.	Original Hb.	Fe retained, %.	Average daily Hb. increase.	Fe utilized, %.
Chronic Hemorrhagic Anemia.				
1	4.34	27.8	0.113	3.2
2	1.55	36.4	0.041	1.2
3	7.68	43.6	0.117	3.4
Average		35.9	0.090	2.6
Idiopathic Hypochromic Anemia.				
1	6.01	51.4	0.056	1.62
2	6.17	71.3	0.037	1.09
3	4.62	50.5	0.117	3.42
Average		57.7	0.070	2.06

of hemoglobin per day as the lower limit of a satisfactory response when the initial hemoglobin is below 7.8 gm. per 100 cc. of blood.[14] There was considerable variation in the amount of iron required to produce this response, and the amount was greater in cases of idiopathic hypochromic anemia than in cases due to chronic hemorrhage.

In experiments on the retention of iron, which are of necessity confined to a relatively small group of cases, we have used iron and ammonium citrates exclusively. When this is administered in a dosage of 3 gm. per day, yielding approximately 500 mg. of metallic iron, the hemoglobin response fell short of the optimum response of Heath. In occasional periods and in certain subjects the response reached this minimum figure, but the average daily increase for the entire period of observation was below this amount. In Table 3 are given the original hemoglobin concentrations, the daily hemoglobin response, and the daily iron retention. It will be noted that there was no definite correlation between the amount of iron retained and the hemoglobin increase. The gastric acidity did not influence the results in this series of cases, and a satisfactory reticulocyte response was obtained in each instance.

Similar studies were carried out in another group of patients to whom only 1 gm. of iron and ammonium citrates was given each day.

Only 3 of these patients were under observation long enough for their hemoglobin response to be of significance, but in these a fairly rapid increase was obtained in spite of the small amount of iron being administered (Table 4).

When these results are viewed in the light of Heath's work, it would appear that the amount of iron being administered was less than the optimal amount. A rapid increase in hemoglobin is advis-

TABLE 3.—IRON RETENTION. IRON INTAKE, 500 MG. PER DIEM.

Case.	Gastric acidity.	Average daily iron retention, mg.	Per cent of iron retained.	Average daily hemoglobin increase, gm.	Reticulocytes, highest reading.	Original hemoglobin, gm. per 100 cc.
1	0	368.9	71.3	0.037	3.4	6.17
2	0	188.9	36.4	0.042	10.5	1.55
3	Normal	133.4	51.4	0.056	1.4	6.01
4	Low	151.0	31.6	0.092	2.0	5.68
5	Low	72.5	14.0	0.095	2.0	5.56
6	Low	140.8	27.8	0.113	5.4	4.37
7	0	225.2	43.6	0.117	1.6	7.68
8	0	261.2	50.5	0.117	8.9	4.62

able in the early stage of therapy and undoubtedly the larger amounts of iron should be employed. However, it is seen from these tables that relatively large amounts of iron were being retained and a fairly rapid hemoglobin rise occurred from these smaller doses of iron. This was especially true when 3 gm. of iron and ammonium citrates per day were being administered; but even with 1 gm. per day, sufficient iron was retained not only for hemoglobin formation

TABLE 4.—IRON RETENTION IRON INTAKE, 170 MG. PER DIEM.

Case.	Gastric acidity.	Average daily iron retention, mg.	Per cent of iron retained.	Average daily hemoglobin increase, gm.	Reticulocytes, highest reading, %.	Original hemoglobin, gm. per 100 cc.
1	0	44.7	27.1	0.082	1.0	7.36
2	Normal	42.6	23.2	0.100	2.8	4.15
3	Normal	82.2	45.1	0.151	5.4	7.80

but also for replenishment of the reserve supply of the body. It was shown that a large percentage of the retained iron was not used immediately in hemoglobin formation, but was stored elsewhere in the body.[11,12] These results indicate that sufficient iron may be retained from these moderate amounts of iron and ammonium citrates to produce a relatively rapid hemoglobin response as well as to replace the depleted iron stores of the body, and these amounts would seem to be adequate in cases where continued iron administration is necessary over a long period of time after the hemoglobin level has returned to approximately normal.

Hydrochloric acid was given to patients receiving a normal iron intake as well as to those receiving 500 mg. of iron per day. The addition of this acid did not increase the iron retention nor the rapidity of hemoglobin regeneration.[1c]

Iron retention experiments were carried out with the metal

administered in combination with copper and with a liver fraction.[1b] It was found that copper, when given with a relatively small amount of iron (approximately 250 mg. per day), produced a marked diminution in the amount of iron retained by the body, but when given with larger amounts of iron (approximately 500 mg. per day), it had no appreciable effect on the storage of iron. In neither case was the hemoglobin response more rapid than was obtained by the use of iron alone. The addition of a liver fraction had a negligible effect on both iron retention and hemoglobin regeneration. From these results it appears that the addition of copper or a liver fraction is unnecessary in the treatment of hypochromic anemias and this is in agreement with the conclusions reached by Bethell.[2] It is possible that copper is essential in hemoglobin formation;[8] but if so, sufficient amounts are obtained from the food, and as a contaminant of iron salts, so that additional amounts are unnecessary. Keefer[16] has shown that certain cases of hypochromic anemia respond better when iron is administered in combination with a liver fraction, but we did not encounter such a case.

The administration of iron is frequently recommended by medical texts to all types of chronic diseases complicated by a "secondary" or hypochromic type of anemia. It has been shown by Heath,[14] Wintrobe,[25] and others that the hemoglobin response to iron is negligible in many of these cases. We have followed the reticulocyte and hemoglobin response in cases of chronic nephritis, carcinoma uncomplicated by hemorrhage, lymphoma, leukemic and aleukemic myelosis, subacute bacterial endocarditis, rheumatic heart disease, and hyperparathyroidism during the administration of iron, and found no response. We believe that there is no justification for its administration in such cases.

The parenteral administration of iron has been recommended in certain instances. Heath[15] has reported that the amount of iron given parenterally corresponds closely to the amount of iron gained in the circulating hemoglobin, and in his cases found an average utilization of 96%. He found that 32 mg. of metallic iron given parenterally was equivalent to 1000 mg. given by mouth. We have determined iron balances on 4 patients to whom the iron was administered intramuscularly.[11b] It was found that although the patients retained the iron when given in a dosage of 12.3 mg. per day in the form of iron and ammonium citrates, none of the 4 showed a significant increase in hemoglobin. Two of the patients were subsequently given 500 mg. of iron per day by mouth, and a satisfactory hemoglobin response ensued. Another patient with ulcerative colitis and an inability to tolerate orally administered iron, received iron intramuscularly with no hemoglobin or reticulocyte response. From our experience, we do not feel that this amount of intramuscular iron is of benefit. We have tried larger amounts, 32 mg. per day, but generalized reactions were so severe that its administration was discontinued. Our conclusions agree with those of Brock[4]

who states that "there is never any indication for injections of iron in the treatment of anemia."

Comment. We have considered the various theories which have been proposed to explain the occurrence of idiopathic hypochromic anemia, and briefly discussed these in the light of experimental evidence obtained during the course of iron retention experiments. From the data presented, we believe that idiopathic hypochromic anemia is essentially due to chronic blood loss, either through normal or excessive menstruation, more frequently the latter, occurring in a patient in whom there is a deficient absorption of iron due to achlorhydria. This leads to a depletion of the normal iron stores in the body, and consequently to a diminished production of hemoglobin, and so to anemia. The hypochromic anemia of pregnancy is essentially the same disease and is produced by the fetal requirements for iron depleting the maternal supplies. This type of anemia not infrequently merges into a typical picture of the so-called idiopathic form. Evidence is presented to show that no derangement of iron metabolism exists in these individuals with idiopathic hypochromic anemia.

With this information, the term "idiopathic" is no longer applicable to this disease, but its use has become so firmly entrenched that it will be difficult to change. Many other terms which have been applied to the condition have obvious disadvantages. The term "simple achlorhydric anemia"[23] is the most satisfactory and should include not only those cases now termed as "idiopathic" but also those cases of menorrhagia and other chronic forms of hemorrhage in which a deficiency in the gastric secretion is present.

Our experiments have demonstrated that a large amount of iron is retained when iron and ammonium citrates are administered in a dosage of 3 gm. per day and agree with the results of Brock and Hunter.[5] The hemoglobin response to this amount of iron is not as rapid as is obtained with larger amounts of iron. With even smaller amounts of the drug, 1 gm. per day, the iron retention is quite large and a fairly rapid increase in hemoglobin ensues. These dosages must be considered as suboptimal when compared to the results of Heath, and larger amounts of iron are undoubtedly advisable early in the course of therapy, especially in the more severe grades of anemia.

It has been repeatedly emphasized that the most satisfactory results in the treatment of this type of anemia are obtained with the use of massive doses of iron, and our results are in no way contradictory to this belief. They do show, however, that a hemoglobin response ensues when smaller amounts of iron are used, so that the massive doses need not be continued indefinitely in order to maintain a satisfactory level. The reasons for the more rapid hemoglobin response which is obtained with excessive amounts of iron has not been adequately explained. We have shown that the amount of iron retained from the smaller doses would be adequate for a satisfactory

response if it were efficiently utilized in the production of hemoglobin. Our results and those of Brock[5] show an excessive retention of iron when larger amounts of iron are administered. Brock[4] has discussed the efficacy of excess iron in more detail and presents evidence that "excess" iron is more effective than "enough" iron, but concludes that "there is at present no rational explanation of the necessity for such large doses."

The addition of copper or of a liver fraction did not increase the rapidity of hemoglobin regeneration in these cases nor did the administration of hydrochloric acid prove to be of benefit. The use of parenterally administered iron in a tolerated dose did not lead to hemoglobin regeneration.

Summary. 1. Idiopathic hypochromic anemia, in most cases, is a chronic hemorrhagic anemia due to menstrual blood loss and an improper absorption of iron due to deficient gastric secretion. There is no evidence of faulty iron metabolism.

2. "Simple achlohydric anemia" is therefore a preferable term.

3. Massive doses of iron produce a more rapid hemoglobin response in hypochromic anemia than do smaller amounts, although 1 gm. and 3 gm. of iron and ammonium citrates per day produce a fairly satisfactory increase in some cases even though achlorhydria is present. These amounts lead to a storage of iron in addition to that used in hemoglobin formation.

4. Neither copper nor a liver fraction, when given in addition to the iron, increased the rapidity of hemoglobin production.

5. Iron, administered intramuscularly in a tolerated dose, did not produce a hemoglobin response.

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STUDIES ON THE ANEMIA OF CHRONIC GLOMERULONEPHRITIS AND ITS RELATIONSHIP TO GASTRIC ACIDITY.*

By Stuart R. Townsend, M.D.,
RESEARCH FELLOW IN MEDICINE, HARVARD MEDICAL SCHOOL,

Edward Massie, M.D.,
ASSISTANT RESIDENT PHYSICIAN, PETER BENT BRIGHAM HOSPITAL,

AND

Richard H. Lyons, M.D.,
MEDICAL HOUSE OFFICER, PETER BENT BRIGHAM HOSPITAL, BOSTON, MASS.

(From the Harvard Medical School and the Medical Service of the Peter Bent Brigham Hospital.)

Ceconi[9] in 1905 was one of the first to suggest that the anemia of nephritis was probably due to a deficiency of the hematopoietic system caused by retained toxins. Since then many investigators have reiterated this theory. Brown and Roth[5] pointed out the lack of correlation between the anemia and blood loss or excessive hemolysis. Parsons[27] and recently Klemperer and Otani,[17] Misske and Otto[23] and others have demonstrated that the anemia develops particularly in the active stages of chronic glomerulonephritis and becomes accentuated as the renal insufficiency and retention of nitrogenous products become more marked. The most popular theory of the production of the anemia seems to be that it is due to depressed hematopoietic activity dependent on the toxic injury, occurring with the renal breakdown.

In the last decade, the study of gastric acidity has become an essential part of the study of any anemia, but most workers have neglected this important phase in their investigations on the anemia of nephritis. The few isolated studies on gastric secretion in nephritis have failed not merely to include uniform methods of determining the gastric acidity but also to present uniform conclusions. Biernacki,[4] von Noorden,[26] Leist and Welkmann[19] and others [10,12,13,15,18,20,21] have found variable degrees of gastric acidity in cases of nephritis. Collectively, their studies revealed that 60% of their cases showed a diminution of the free acid present. No attempt has been made by anyone, as far as we can discover, to show any correlation between gastric acidity and the anemia.

Practically all previous investigations on the anemia of nephritis have been made with consideration only of the red cell counts, hemoglobin levels, calculated uncorrected color indices and blood nitrogen figures. Berg,[3] Aubertin and Yacoel[2] have drawn attention to certain cases with high color indices and ascribed them to an existing hyperchromic anemia. Most authors have classified the anemia

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as belonging to the "secondary group," a term which seems unsatisfactory because those formerly so classified differ widely in their findings and in response to various types of therapy. In recent years, studies on the various anemias have been made by Osgood and Haskins,[28,29] Murphy,[25] Wintrobe[33a,b] and others using a uniform hematologic technique which now allows investigators to distinguish four types of anemia; 1, macrocytic, characterized by an increase of the mean volume and hemoglobin content of the red cells; 2, normocytic, where the size and hemoglobin of the red cells are within normal limits; 3, simple microcytic, distinguished by a moderate reduction in the size and slight reduction in the hemoglobin content; and, 4, hypochromic microcytic, where the red cell count is reduced slightly but the size of the cell is small and the hemoglobin much diminished. The following table lists the values for these types of anemia:

TABLE 1.—VALUES IN FOUR TYPES OF ANEMIA (WINTROBE).

Type of anemia.	MCV* (cu. micra).	MCH* (micro-micrograms).	MCHC* (%).
Macrocytic	95–160	30–52	31–38
Normocytic	80– 94	27–32	33–38
Microcytic	72– 79	22–26	31–38
Hypochromic	50– 72	14–21	21–29

* MCV = Mean corpuscular volume; MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration.

Such studies have been of value in diagnosis and often in indicating the type of treatment which might be expected to produce results. Since previous studies on this phase of nephritis have failed to utilize these more accurate methods, we felt that the application of this hematologic technique to our patients would enable us to classify their anemias more definitely, might give some clue toward recognition of the fundamental defect present in the anemia of nephritis and possibly might suggest a more efficacious treatment. Besides we felt that an assessment of the gastric acidity, along with these studies might prove illuminating. Possibly they might disclose some correlation between the developing anemia, nitrogen retention, and diminishing gastric acidity. The refractory nature of the anemia to iron therapy has always been a puzzling one and suggests that such medication may fail because of a disturbed gastric secretion.

In planning this study on the anemia of nephritis, it was apparent therefore that several questions had to be answered, namely, the nature of the anemia, the type of the red blood cell, the relationship of the anemia to nitrogen retention and renal insufficiency, the state of the gastric secretion, the reason for the lack of response to iron and what evidence there is for the theory of depressed hematopoietic activity. Consequently our plan of investigation included: 1, red cell counts; 2, hemoglobin determinations; 3, cell volumes; 4, calculations of the mean corpuscular volume, mean corpuscular hemo-

globin, and mean corpuscular hemoglobin concentration; 5, blood nitrogen determinations; and, 6, gastric analysis.

Methods. Blood was withdrawn, without stasis, from the median basilic vein with a dry syringe and needle. The blood was placed in a small test tube containing powdered heparin and gently mixed by inversion, care being taken to avoid small clots.

Red cell counts were made, using standardized red blood cell counting pipettes, counting chambers and cover slips. Three independent dilutions were made, and when necessary more, counts only being used where the variations were not greater than 100,000.

Hemoglobin determinations were made using the Evelyn photoelectric colorimeter[11] and the methods he describes. These were checked occasionally by Van Slyke's oxygen capacity method.

Cell volumes were estimated from hematocrit tubes,* readings being made after centrifuging at 3000 revolutions per minute for 30 minutes, to obtain constant volumes.

From the values for red blood counts, hematocrits, and hemoglobin contents, the mean corpuscular volume, mean corpuscular hemoglobin, and mean corpuscular hemoglobin concentration were calculated as follows:[30c]

$$\text{Mean corpuscular volume (MCV)} = \frac{\text{Hematocrit \%} \times 10}{\text{Number of R.B.C. in mils.}}$$

$$\text{Mean corpuscular hemoglobin (MCH)} = \frac{\text{Gm. hemoglobin per 100 cc.} \times 10}{\text{Number of R.B.C. in mils.}}$$

$$\text{Mean corpuscular hemoglobin concentration (MCHC)} = \frac{\text{Gm. hemoglobin per 100 cc.} \times 100}{\text{Hematocrit \%}}$$

The non-protein nitrogen was determined on fasting bloods using the micro-Kjeldahl method.

Gastric analysis was performed using 50 cc. of 8% alcohol as a test meal and the total and free acidity determined by titration with 0.1 N. NaOH, using Töpfer's reagent and phenolphthalein as the indicators. Hydrochloric acid responses to the test meal were checked by histamine injection. Normal levels of gastric acidity were regarded as the equivalents of 20 cc. and 40 cc. of 0.1 N.HCl following alcohol and histamine respectively.

Unselected patients were taken from the wards and the Renal Vascular O.D. Clinic. Their ages represent all decades, 50% being under 35 years.

Of our 48 cases of chronic glomerulonephritis, 27 had red cell counts above 4,000,000 and 21 had counts below this level. The first group will be referred to as the non-anemic and the second as the anemic group.

The majority of the patients presented pallor of the skin and mucous membranes and it was surprising to find that only 43.5% of the cases had a red cell count below 4,000,000. As one would expect, the blood picture of those without anemia was a normocytic one. The average count was 4,850,000, hemoglobin 92% (14.5 gm.) and a

* Pyrex tube calibrated to hold 2 cc. and volumetrically graduated into ten divisions reading from the bottom of the tube 0–10. Each of these is further divided into ten equal graduations, with four similar graduations above the 10 mark to permit reading in case of overfilling. The total graduated distance was not over 11 cm. The total height did not exceed 12.5 cm. The inside bore of the tubing used is approximately 5 mm.

cell volume of 43.9%; the calculated mean corpuscular volume was 90, the mean corpuscular hemoglobin 29, and the mean corpuscular hemoglobin concentration 33 (Normal MCV 80–94, MCH 27–32, MCHC 33–38). However, the hemoglobin content in individual cases was at the extreme lower limit of normal and, in many cases, at the upper limit of figures associated with the microcytic type of red cell. While these non-anemic cases exhibited the necessary

TABLE 2.—RESULTS.

	Age.	R.B.C.	Hgb., %.	*Hgb., gm.	Hematocrit, %.	MCV.*	MCH.*	MCHC.*	N.P.N., mg. %.	Free HCl.	Total acid.	PSP.	CO_2 content, vols. %.
Non-anemic males:													
Average (16 cases)	12–46	4.94	96	15.1	44.6	90	30	33	34	22	31	51	50.1
Non-anemic females:													
Average (11 cases)	17–59	4.72	88	13.7	42.9	90	29	32	33	15	24	48	50.6
Anemic males:													
Case No.													
28 . . .	16	3.68	70	10.9	31.1	84	31	35	46	6	20	40	49.9
29 . . .	47	3.36	57	10.8	30.8	91	32	35	80	7	17	10	38.9
30 . . .	45	3.19	58	9.1	26.0	81	28	35	74	0	10	..	39.0
31 . . .	46	2.28	46	7.8	20.5	90	29	37	116	0	9	0	29.9
32 . . .	39	2.00	38	5.8	16.0	80	29	36	130	0	10	0	29.8
33 . . .	47	2.78	49	7.6	26.2	94	27	29	70	6	15	7	50.5
34 . . .	26	1.93	37	5.7	17.4	90	29	33	130	0	15	0	10.1
35 . . .	15	2.89	49	7.6	22.4	84	26	34	39				
36 . . .	48	3.61	67	10.4	31.2	86	28	31	58	0	15		
37 . . .	17	1.81	29	4.5	16.2	89	25	28	89	0	9	0	27.8
38 . . .	41	1.75	27	4.2	15.0	86	24	28	180	0	14	0	28.0
Average (11 cases)	15–48	2.66	48	7.7	22.8	87	28	33	92	2	13	7	33.7
Anemic females:													
Case No.													
39 . . .	18	3.81	73	11.3	34.0	89	29	33	41	0	10	30	48.2
40 . . .	34	3.39	66	10.3	32.3	95	30	31	86	3	19	2	33.5
41 . . .	69	2.74	54	8.5	26.7	97	31	32	75	0	17	0	24.0
42 . . .	66	2.18	44	6.9	19.6	90	30	32	82	0	9	0	19.4
43 . . .	59	3.50	59	9.2	31.2	89	26	29	46	0	12	15	44.0
44 . . .	47	3.59	59	9.2	32.3	89	25	28	57	16	24	40	
45 . . .	16	3.97	67	10.4	37.3	93	26	28	36	..	..	55	
46 . . .	24	3.83	61	9.5	34.8	89	25	27	36	10	18		
47 . . .	36	3.75	60	9.4	32.0	85	24	29	47	11	21	50	
48 . . .	39	3.30	55	8.6	27.5	83	26	31	105	0	17	3	49.7
Average (10 cases)	16–69	3.41	60	9.3	30.8	90	27	30	61	4	16	22	36.5

* As in Table 1.

findings for the diagnosis of chronic glomerulonephritis, as one would expect, they did not exhibit marked diminution of renal function or any degree of nitrogen retention.

The anemic group presented the characteristics of a normocytic anemia, the cell size being within normal limits. The average red count of this group was 3,010,000, hemoglobin 54% (8.46 gm.) with a cell volume of 26.6%. It will be noted that the average mean

corpuscular volume is 88, mean corpuscular hemoglobin 28, and the mean corpuscular hemoglobin concentration 31, this average fitting a true normocytic anemia. As stated above, there were a large portion of the anemic patients who had a low hemoglobin content, although the cell size was normal. Our findings of a normocytic anemia confirms Wintrobe's observations which he made on cases of nephritis included in his studies on anemia. In this group we found no cases with a definite macrocytosis.

In contrast to the non-anemic group, these patients with chronic glomerulonephritis exhibited obvious impairment in renal function and varying degrees of nitrogen retention. It is this last point, the degree of nitrogen retention, that has interested most of the previous authors in discussing the anemia of nephritis. Assuming that the anemia was due to a toxic substance, they made an effort to determine whether one of the normal metabolic products retained in blood in excessive amounts was the cause of the toxic depression of the hematopoietic activity or whether it was an unknown toxic agent which was directly responsible. They found that the retention of nitrogen bore a close relationship to the degree of anemia when individual cases were followed and used this parallelism as an argument favoring the toxic theory. As our experience in our own clinic confirmed this observation, we were interested in determining if the same relationship held for a group of cases. In Table 3 we have tried to illustrate this parallelism.

TABLE 3.—AVERAGE CHANGES OF RED BLOOD CELLS, HEMOGLOBIN AND NON-PROTEIN NITROGEN IN 48 PATIENTS WITH CHRONIC GLOMERULONEPHRITIS.

Hgb. %	100+	90–99	80–89	70–79	60–69	50–59	40–49	30–39	20–29
R.B.C.	5.21	4.78	4.57	4.29	3.86	3.28	2.53	1.96	1.78
N.P.N.	29	35	39	37	55	73	77	130	135
No. cases	10	7	7	6	4	6	4	2	2

It is readily seen that the anemia does progress and becomes accentuated as the degree of nitrogen retention increases.

In individual cases, however, we noted that the degree of anemia and the degree of nitrogen retention for one individual did not hold for another. In a small number of cases there was a definite anemia of moderate grade but without any nitrogen retention whatsoever. Similarly, there was a small number of cases with nitrogen retention but without anemia. However, the average when grouped did show a parallelism between the degree of anemia and degree of nitrogen retention. There is one objection which must be admitted and that is, that we have fewer cases in the most marked degrees of anemia. In spite of this, we feel from our experience and that of others, that the above parallelism holds.

As the degree of nitrogen retention mirrors to some extent the degree of acidosis present, there is reason to suspect that gastric secretion may be disturbed, as the plasma bicarbonate would be utilized in an attempt to regulate the acid-base equilibrium. That

plasma bicarbonate is intimately associated with formation of free hydrochloric acid in the gastric secretion was shown by the work of Apperly and Crabtree[1] and confirmed by Browne and Vineberg.[6] With this thought in mind gastric analysis was performed on 41 of our patients. The degree of the acidity of the specimens taken 1 hour after the alcohol test meal was calculated. All responses were checked with histamine, and blood CO_2 content determinations were carried out.

In the non-anemic group, 22 out of 27 patients had a normal average gastric acidity to the alcohol test meal, 5 cases had an anacidity but showed a response to histamine. This anacidity after alcohol represents an incidence of 18.5%. In these 22 patients, we found that there was a close parallelism with the red cell count but none to the plasma bicarbonate.

In the anemic group, 19 cases were studied. Their responses to the alcohol meal were all diminished and 11 patients (57.8%) showed anacidity to alcohol stimulation and a diminished response to histamine. Five of these 11 cases had absolute achlorhydria even after histamine, an incidence of 26.3% of the 19 cases studied. The carbon dioxide content (plasma bicarbonate) in the anemic group varied from 10 to 50 vols. %, but the most striking feature occurred in the 5 cases with absolute achlorhydria. In these patients the CO_2 content was below 30 vols. %. Browne and Vineberg,[6] using dogs, found that experimentally when the CO_2 content was lowered below 30% that nervous stimulation failed to produce a secretion of free acid. In a small number of cases of chronic glomerulonephritis we have found proof that there is no secretion of hydrochloric acid when the CO_2 content falls below 30% and also that there is a disturbance in gastric secretion even above this level, although there is no relationship to the plasma bicarbonate to indicate that any disturbance in its value is responsible for the diminution of the free hydrochloric acid present.

In Table 4 we have tried to illustrate the relationship between

TABLE 4.—AVERAGE CHANGES OF RED BLOOD CELLS, HEMOGLOBIN AND FREE HYDROCHLORIC ACID IN 41 PATIENTS WITH CHRONIC GLOMERULONEPHRITIS.

Hgb. %	100+	90–99	80–89	70–79	60–69	50–59	40–49	30–39	20–29
R.B.C.	5.10	4.87	4.78	4.27	3.64	3.28	2.41	1.96	1.78
Free HCl	24	20	10	9.5	8	4	2	0	0
No. cases	10	5	4	5	4	6	3	2	2

red cells and hemoglobin to the free acid present in the stomach. It will be clearly seen, again acknowledging the paucity of numbers in the severe grades, that the anemia increases almost in direct relationship to the fall in gastric acidity. This is suggestive at least that the secretion of free HCl is distributed and may bear some relationship to the development of the anemia or at least to its continuance on the basis of improper absorption of materials necessary for blood formation.

It was thought at this point that bone-marrow studies might throw some light on the problem. At least one should be able to determine whether there was any absolute evidence of depressed hematopoietic function. Bone-marrow sections, 31 in all, were reviewed from postmortem material available. This group comprises 20 males and 11 females, of ages varying from 12 to 70 years, with a fairly uniform distribution of age groups. Blood counts done during the course of the disease, in the ordinary routine manner, varied between 1,430,000 and 4,700,000 with low hemoglobin contents. These cases were all clinically and pathologically consistent with the diagnosis of chronic glomerulonephritis, although in some of the older patients there existed secondary disorders not of a nature to interfere with the blood picture. The majority of these patients revealed postmortem rib marrow of a normal or hyperplastic type, and in a few cases where the femur marrow was examined, some increase in the erythropoietic activity. The hyperplasia was generally of the normoblastic type—a functional hyperplasia, commonly associated with chronic infections. In no case was there increased erythropoiesis of the megaloblastic type, such as seen in pernicious anemia, nor were there any abnormalities in the size of the medullary cavity and no evidence of bone absorption. One must bear in mind, however, that these sections are postmortem material and have all the disadvantages of such unit studies. We believe, however, that bone-marrow biopsy would reveal little difference in the histologic picture.

In seeking another possible explanation for the low gastric acidity we studied sections of stomach from 29 of these patients. The studies revealed no histo-pathologic explanation for a diminution of the gastric acidity, although many cases died in acidosis and uremia. The glands were well preserved. The most striking feature was edema of the submucosa and marked anatomical changes in the arterioles of the submucosa: these showed moderate to marked fibroblastic proliferation of the intimal layers producing variable diminution of the lumen. In rare cases, one found occasional vessels occluded by intimal thickening or a thrombus. In these latter cases superficial ulceration was common.

Discussion.—Since there is no evidence to date of increased hemolysis or increased blood loss to explain the anemia of chronic glomerulonephritis, we would expect that it would be due to one or two causes; 1, insufficiency of active blood-forming tissue, or, 2, insufficiency of material available for the production of red cells and hemoglobin.

If the anemia is due to toxic depression of bone marrow one would expect a hypoplastic or aplastic bone marrow. Our studies of postmortem material clearly indicate that the bone marrow is either normal or hyperplastic in appearance, apparently capable of response and containing the cellular elements necessary for erythropoiesis.

This is not in agreement with the recent work of Isaacs,[14] who thinks that the bone marrow in chronic nephritis is aplastic in character.

Our observations on the character of the red blood cell in the anemia of chronic glomerulonephritis permit us to classify the anemia as one of the normocytic variety; but in some of the individual cases, the hemoglobin content is slightly lower than that commonly associated with this type of anemia. A deficient supply of erythrocytic-building material might be considered the possible explanation for this type of picture. It is common knowledge that the anemia of chronic glomerulonephritis does not respond to iron and the slightly lower hemoglobin found in the individual red cell is probably of significance and compatible with our feeling that the anemia is due to a deficiency of blood-cell forming material. Our studies on the gastric acidity have tended to support this view.

Apperly and Crabtree[1] in 1931 suspected that the chemical condition of the blood had some relationship to gastric function and proceeded to show that the amount of HCl present during gastric stimulation was determined or at least bore a close relationship to the bicarbonate content of the blood plasma and could be made to vary by producing changes in the latter. This work was confirmed by Browne and Vineberg[6] in conclusive experiments on dogs. They showed that the secretion following vagal stimulation was inhibited when the CO_2 content of arterial plasma fell below 30 vols. %. They further demonstrated that total amount of acid secreted, as well as the concentration, could be increased or decreased by artificially raising or lowering the plasma CO_2 content. Their work strongly suggests that the plasma bicarbonate is involved in some manner in the production of HCl.

In nephritis, we have a pathologic condition existing in the kidneys which prevents the normal elimination of the end products of protein metabolism and the normal regulation of the acid-base equilibrium, especially in the chronic active and terminal stages with renal insufficiency. When sufficient renal impairment occurs to produce nitrogen retention, there is also an accompanying disturbance in the acid-base control of the body and a degree of acidosis is developed which clinically is not detectible and which varies with the nitrogen retention. In these stages, as we have pointed out before, the anemia becomes most marked and progressive, the blood nitrogen increases, acidosis occurs, gastric acidity becomes lower and at a point is not secreted at all. We found, however, that often there is a lower gastric acidity than can be accounted for by the blood bicarbonate; but that in the terminal stages, when the CO_2 content was below 30 vols. %, there was complete anacidity even after the use of histamine. To us one of the most important features in the anemia of chronic glomerulonephritis is the diminished or absent HCl in the gastric secretion and this diminution must play an important part in the improper digestive processes and improper absorption of food and iron.

Gastric digestion, by virtue of the presence of free hydrochloric acid and pepsin, has a definite action in: 1, hydrolysis of protein; 2, modification of the pH of the small bowel, and, 3, as a stimulation for the secretion of pancreatic enzymes and flow of bile. These are all necessary to carry on the proper digestive processes in the remainder of the gastro-intestinal tract. Many in the past have believed that this function has not been entirely necessary for the continuous well being of patients. Surgery has taken advantage of this assumption and has performed gastric resections of varying degrees up to total gastrectomy. In the last few years, however, we have learned that many of these patients develop an anemia of various types.

Experimentally, too, in recent years gastric digestion has been shown to be of the greatest importance in relation to anemia. Castle[7,8] and others have called attention to the absence of hydrochloric acid in the stomach in the anemias of other types and have concluded that various disturbances of the gastro-intestinal tract may interfere with digestion and absorption necessary for proper metabolism of food substances required for hematopoietic activity, even in the presence of a normal diet.

Mettier and Minot[22] then indicated that soluble iron compounds are more readily absorbed in the presence of acid meals. This corresponded closely with the work of Mitchell and Miller,[24] who were more concerned in the most suitable pH for iron utilization. Kellogg and others[16] have recently succeeded in showing that when the iron reserves of the body were depleted, a condition of hypochromic anemia results and persists in the absence of normal gastric secretion, even when an iron rich diet is ingested.

From a therapeutic standpoint, predigested acid meals, or even hydrochloric acid itself, might prove of value, except there are obvious reasons to believe that such measures would only serve to increase the acidosis present.

In conclusion, our investigations, along with the experimental work of others, seem to indicate that there is a correlation between the decreased renal function, the development of a normocytic anemia and the development of a low to absent secretion of free hydrochloric acid. The low gastric acidity, by interfering with the proper metabolism of ingested food and the absorption of iron, indirectly produces a deficiency of "building material" for sufficient red blood cell formation and the production of hemoglobin. While we have not demonstrated the etiologic factor in the production of the anemia of chronic glomerulonephritis, we have indicated reasons for the continuance of the condition and possibly one of the factors responsible for the refractory response to therapy.

Summary. 1. The anemia of chronic glomerulonephritis is normocytic in type.

2. The anemia becomes manifest as renal insufficiency occurs and increases with the degree of nitrogen retention.

3. With increasing anemia, there is a decrease in the gastric acidity.

4. Absolute achlorhydria is present when the CO_2 content of whole blood (plasma bicarbonate) falls below 30 vols. %.

5. There is no apparent lack of active blood forming tissue.

6. A discussion of the relationship between renal insufficiency, gastric acidity and the anemia has been given.

7. Reasons have been offered for the persistence of the anemia and its refractoriness to therapy.

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DEFICIENCY SYNDROMES ASSOCIATED WITH CHRONIC ALCOHOLISM.

A Clinical Study.

By John Romano, M.D.,

Commonwealth Fund Fellow in Psychiatry; Assistant Physician, Colorado Psychopathic Hospital, Denver, Colorado.

(From the Colorado Psychopathic Hospital.)

Lettsom[8] (1787) first described alcoholic polyneuritis and attributed it to the neurotoxic effect of the alcohol. This belief remained unchallenged until Shattuck,[12] in 1928, suggested vitamin deficiency as a probable cause of the neuritis. Since then Minot,[10] Wechsler,[15] and Meyer[9] have discussed the relationship of avitaminosis to this disorder. From observations of 57 cases and a study of the record

of 73 additional cases Minot, Strauss, and Cobb[11] concluded that dietary deficiency (B_1) played an important rôle in the production of "alcoholic" polyneuritis. In addition to inadequate intake they believed that other factors such as the states of the gastro-intestinal tract were operative in the production of the neuritis. In an excellent review, Cobb and Coggeshall[3] drew attention to the diversity of lesions in the central and peripheral nervous system of chronic alcoholics, and speculated that "the imbibing of alcohol may, by its effect on the digestive tract and the diet, precipitate neuronal degeneration (and perhaps vascular lesions) in the brain, cord or peripheral nerves. If the process is largely in the brain and peripheral nerves, Korsakoff's syndrome results. If the brain is affected severely, with less degeneration of the cord and least in the peripheral nerves, the syndrome is that of pellagra. The converse of this picture is 'alcoholic' polyneuritis, while Nonne's 'myelitis intrafunicularis' is intermediate between these two."

In this connection Spies[13] and his coworkers have contributed significant data in respect to the similarity between endemic pellagra and "alcoholic" pellagra and the dramatic response of the latter group to vitamin B_2 therapy.

To each of 10 alcoholic addicts with polyneuritis, Strauss[14] gave a pint to a quart of blended whisky daily. He supplemented a vitamin-rich diet with oral administration of yeast, and parenteral introduction of vitamin B_1 and liver. He observed that the neuritis improved as rapidly with alcohol as without it and concluded that the "alcoholic" polyneuritis did not result primarily from a direct neurotoxic effect of alcohol but was probably dependent upon dietary deficiency. Jolliffe, Colbert, and Joffe[7] estimated the vitamin/calory ratio (Cowgill's[4] formula) of 42 alcohol addicts, 26 of whom had polyneuritis. They demonstrated that alcohol addicts with polyneuritis failed to obtain adequate amounts of vitamin B while those without polyneuritis, though the addiction was of long duration, did obtain adequate amounts; and that certain subjects without polyneuritis consumed enough alcohol over an adequate period of time to cause peripheral nerve involvement due to the alcohol *per se*. In a later publication,[6] these authors noted the effects on 28 alcohol addicts who had uncomplicated polyneuritis of: 1, an inadequate or borderline vitamin B diet; 2, a diet with approximately twice the estimated vitamin B requirement; and, 3, a diet with approximately 4 times the vitamin B requirement. Those in the first 2 groups showed no improvement in the course of a month; improvement was more marked in those of the 3d group than in those of the 2d.

In addition to the qualitative and quantitative studies of vitamin B deficiency in alcohol addicts with polyneuritis, Blotner[2] has demonstrated the inhibitory effect of alcohol on the proteolytic activity of certain gastro-intestinal enzymes *in vitro* and *in vivo*.

Since the appreciation of the avitaminotic aspects of chronic alcoholism has many practical therapeutic considerations it appeared of value to undertake a clinical study of the incidence of polyneuritis in the alcohol addicts admitted to this hospital. Particular attention was given to the dietary history, anemia, and the clinical response to vitamin B therapy.

Clinical Study. A study was made in this Hospital from September 1, 1935 to August 31, 1936, of the total number of patients admitted in whom chronic alcohol addiction had played a major rôle in causing their admission. Of the total first admission (844) during this period, 131 patients were examined (15.5%). Together with the usual physical, neurologic and psychiatric examinations, particular attention was paid to the dietary history, presence or absence of polyneuritis, anemia and clinical response to vitamin B therapy.

It is not the purpose of this paper to discuss in detail the symptomatic rôle that alcohol addiction plays in the personality instability of the individual patient. Suffice it to say, as has been noted previously,[5] that chronic alcoholism *per se* is not a disease, rather it is a manifestation of an underlying personality maladjustment and that remedial measures to be successful must be directed at the primary and significant causal factors. Any attempt to treat chronic alcoholism must be based on an intelligent appreciation and evaluation of the endowment, the life experiences, and the specific situations in which the individual patient finds himself. This can only be done with a detailed personality analysis in the hands of well trained physicians over a long period of time and with the patient in a controlled environment.

Every patient who was studied has been addicted to the use of alcohol for varying lengths of time preceding admission to the hospital. It was extremely difficult to come to any reliable conclusion concerning the number of years of addiction. Inquiries were made in respect to quantity, quality and frequency of the liquor consumed but the data does not warrant any reliable conclusions.

Age Incidence. It is interesting to note that the age period between 30 and 50 contained over 64% of the total number (Table 1).

Table 1.—Age Incidence of Total Number of Patients.

21 to 30	16
31 to 40	44
41 to 50	41
51 to 60	20
61 to 70	8
71 to 80	2
	131

Sex Incidence. Of the 131 cases, 16 (12.2%) were female. Although this small number does not warrant any valid statistical conclusions, the age incidence when divided as to sex reveals a

relative increase in the number of females of a later age period (41 to 50) as compared with the males and with the total number.

TABLE 2.—SEX INCIDENCE.

	Female.	Male.
21 to 30	3	13
31 to 40	4	40
41 to 50	8	33
51 to 60	1	19
61 to 70	..	8
71 to 80	..	2
	16	115

Mental Status. Ebaugh and Romano[5] have discussed the inadequacies of the present classification of the alcoholic psychoses. The various dramatic incidents that are experienced by chronic alcoholics such as pathologic intoxication, delirium tremens, acute and chronic alcoholic hallucinosis and Korsakoff's psychosis have addiction to alcohol as a common denominator although the presence or absence of personality predisposition, more profound mental instability and somatic factors (avitaminosis) may have a more important causal relationship. This classificatory inadequacy is most evident in a consideration of chronic alcoholism, uncomplicated by the previously noted psychotic incidents. Previous concepts of "chronic deterioration," "alcoholic paranoia" and others have only provoked further confusion. An attempt[5] has been made to divide this group into etiologic divisions, although this is far from being satisfactory.

TABLE 3.—INCIDENCE OF PSYCHOSES.

	Male.	Female.
Pathological intoxication	1	0
Chronic alcoholism with mental deficiency (moron)	0	1
Chronic alcoholism with senile dementia	2	0
Chronic alcoholism with Korsakoff's psychosis	2	5
Chronic alcoholism with manic-depressive depression	3	1
Chronic alcoholism with schizophrenia	8	0
Chronic alcoholism with cerebral arteriosclerosis	11	0
Chronic alcoholism with psychosis	14	0
Chronic alcoholism with delirium tremens	18	3
Chronic alcoholism without psychosis	56	6
	115	16

Dietary History. Attention was paid to the quantity and quality of the patient's diet. While it was almost impossible to secure reliable data in respect to the dietary history during the total period of addiction an attempt was made to investigate the peculiarities of the food intake for the period preceding admission. Informants as well as the patient were contacted for these data. By the arbitrary divisions of mild, moderate, and severe are understood qualitative dietary inadequacies for periods varying between 2 weeks and 6 months preceding hospital admission. The accompanying tables show that 11 (68.7%) of the females and 64 (55.6%) of the males had some qualitative inadequacy in their diets for varying

periods previous to admission. It is more pertinent to remark that of the 77 patients (58% of total number) who showed evidence of some form of neuritis 61 (79%) gave a history of inadequate diets.

TABLE 4.—INCIDENCE OF DIETARY INADEQUACY.

	Male.	Female.
No data	33	2
Normal	18	3
Mild	39	2
Moderate	22	3
Severe	3	6
	115	16

Incidence of Polyneuritis. Although it is difficult to divide or classify the severity of the neuritides observed, it was thought expedient to introduce arbitrary divisions of mild, moderate and severe. Obviously, what was interpreted as mild on one examination may have been designated moderate or severe in following examinations. However, the neurologic status on admission as interpreted by one examiner was considered the basis for the classification. By mild is understood the presence of pain, deep muscle tenderness and weakness, superficial hyperesthesia and exaggerated deep reflexes. With increased weakness, persistent deep muscle pain, beginning muscle atrophy, paresthesia, disturbance of position and vibration senses and loss of deep reflexes, a moderate degree of involvement is present. Muscle atrophy or paralysis, with or without contractures, "glove and stocking" anesthetic areas, vibration and position sense disturbances and absence of deep reflexes constituted the more advanced or severe degree of nerve involvement. In the severely involved of the female group, 5 of the 6 experienced a Korsakoff's psychosis. Dermatitis with pigmentation, glossitis, and stomatitis together with intractable diarrhea were observed in 4 of these 5 and suggested deficiency of vitamin B_2. While spongy gums were observed frequently in both male and

TABLE 5.—INCIDENCE OF POLYNEURITIS.

	Male.	Female.
Normal	48	6
Mild	31	2
Moderate	22	2
Severe	14	6
	115	16

female patients no definite clinical evidences of scurvy were noted. Unfortunately, gastric analyses were not done of the majority of the patients studied and the conclusions do not warrant mention. Ten (62.5%) of the female patients, 67 (58.2%) of the male patients suffered from some degree of peripheral nerve involvement. Of the total number of patients studied (131), 77 (58%) presented evidences of neuritic involvement.

Anemia. Accepting the standards as determined by Andresen and Mugrage[1] for red blood cell values for normal men and women in this region, the initial red blood cell count and hemoglobin determination (Sahli) taken on admission were collected in order to determine the incidence of anemia in these patients. The following are the standards that were used for comparison (Table 6.)

TABLE 6.—ANEMIC STANDARDS.

	Men.				Women.			
	Normal.	Mild.	Moderate.	Severe.	Normal.	Mild.	Moderate.	Severe.
Hemoglobin (grams) Sahli	14.0–19.0 mean 16.5	12.0–14.0	10.0–12.0	Below 6	12.5–16.5 mean 14.5	11.5–12.5	9–11.5	Below 6
Red blood corpuscles (millions)	4.7– 6.2 mean 5.4	4.4– 4.7	3.4– 4.4	Below 2	4.2– 5.1 mean 4.6	3.8– 4.2	3.0–3.8	Below 2

Eleven (68.7%) of the female patients, and 64 (55.6%) of the male patients suffered from some degree of anemia, although 56 of the total number of patients (75) with some degree of anemia had only mild involvement. Of the 19 patients who had moderate or severe anemia, 6 (8% of the 75 patients with anemia) had macrocytosis as revealed by increased cell diameter and volume index.

Iron and ammonium citrate in large daily doses (4 to 8 gm.) together with parenteral liver were successful in treating the anemias.

TABLE 7.—INCIDENCE OF ANEMIA.

	Male.	Female.
Normal	51	5
Mild	50	6
Moderate	12	4
Severe	2	1
	115	16

Clinical Response to Vitamin B Therapy. Every patient with either mild, moderate or severe peripheral nerve involvement was placed on a high-caloric, high-vitamin diet (4000 to 5000 calories daily) increasing the quantity of lean-meat protein and decreasing carbohydrate. This diet was supplemented with dried brewer's yeast tablets (4 gm. daily), wheat-germ preparations (30 to 60 gm. daily) and either vitamin B_1 or liver* preparations given parenterally in daily doses. In addition to this, fresh orange or tomato juice together with various preparations of cod-liver oil or haliver oil were given.

In the more severe neuritides associated with Korsakoff's psychoses, forced feedings were resorted to and the parenteral liver dosage was increased (2 to 4 cc. daily).

Due to the variation in severity of the lesions, the individualiza-

* Courtesy of Eli Lilly & Co., Indianapolis.

tion of therapy and the relatively limited stay of the patients (average 24.67 days) adequate quantative data are not available. However, a rough clinical estimate of no change, partial improvement and total improvement was tabulated. Seventy-seven patients (58% of the total number) revealed some evidence of polyneuritis; 5 (6.4%) showed no clinical response to therapy while they were under observation; 47 (61%) showed partial improvement and 25 (32.4%) showed complete improvement.

TABLE 8.—RESPONSE OF THE PATIENTS WITH MILD POLYNEURITIS TO VITAMIN B THERAPY.

	Mild P.	Moderate P.	Severe P.
No change	2	2	1
Partial improvement	14	14	19
Total improvement	17	8	0
	33	24	20

Summary. One hundred and thirty-one chronic alcoholics (15.5% of the total hospital admissions (844) in 1 year) were studied in respect to the incidence of polyneuritis, with particular attention to dietary history, anemia and response to vitamin B therapy.

Of these chronic alcoholics 77 (58%) presented some degree of neuritis.

A history of inadequate food intake previous to admission was obtained in 61 (79% of those showing polyneuritis).

Some degree of anemia was present in 75 (57% of the chronic alcoholics), although 56 (74.6%) had only mild involvement.

Of the 77 patients with neuritis, 5 (6.4%) failed to respond to vitamin therapy, 47 (61%) showed partial improvement, and 25 (32.4%) showed complete improvement with specific therapy during their period of hospitalization.

Conclusion. Vitamins B_1 and B_2 are of definite value in the treatment of the deficiency syndromes associated with chronic alcoholism.

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CASE FINDING IN TUBERCULOSIS, AN ADULT PROBLEM.*

By H. R. Edwards, M.D.,
DIRECTOR, BUREAU OF TUBERCULOSIS, DEPARTMENT OF HEALTH, CITY OF NEW YORK.

Case finding in tuberculosis has been the keynote of the anti-tuberculosis campaign for the past 30 years or more. Throughout this period we have placed increasing emphasis on early diagnosis, but until recently we have made little progress in this direction. The average tuberculosis program involves the examination of contacts to known cases. This is the best and most productive source of case finding thus far developed. Considerable time and emphasis has been placed on routine tuberculin testing and the Roentgen ray in grade-school populations. To date we have accumulated a vast amount of information from such studies. They have been the means of finding many new cases, but if evaluated in the light of the relative yield for the dollar invested there is much reason to question its value, especially if such a plan is the predominant effort at case finding and control in the community.

Fortunately, we are able to clearly evaluate our problem in tuberculosis. It may be done by simple statistical analysis of our cases and deaths by age groups, sex, occupation or other major divisions. The plotting of these data at once indicates a typical curve for either sex. Among females since 1900 we note in general a definite decrease for all ages and for the individual age groups. There is this difference, however, the peak of mortality has shown a tendency to shift forward, so that where it was reached at about the age of 35 in 1900 it is now reached at 25 years. Furthermore, after the sharp rise beginning at 15 years there is now a tendency to flatten out and remain more or less constant for the remaining years of the life cycle.

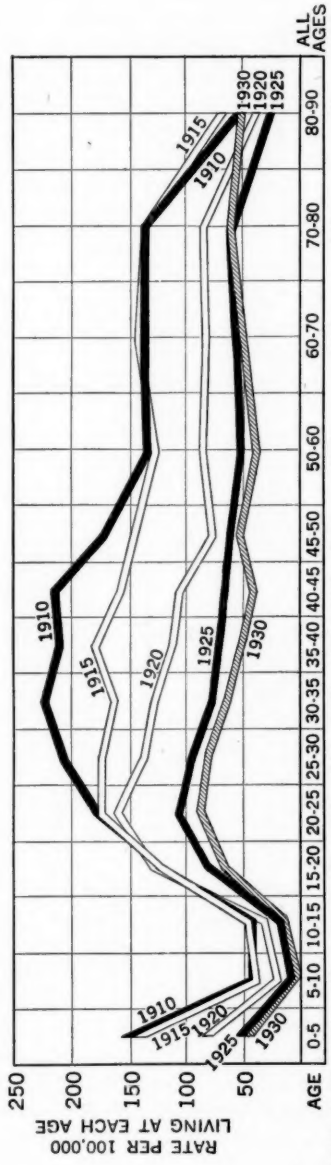
For males we have always noted a much higher rate than among females. In the past 30 years there has been a sharp decline for all ages as well as for the various age periods. In contradistinction to the female curve we note that the peak in mortality in 1900 was at 45 years and in 1930 it has shifted back to 60 years. Also the peak among males is much sharper and falls more abruptly afterward than that for females.

If a similar analysis is made for white and colored we at once note a sharp distinction between the two. The white is invariably lower than the colored.

On the basis of tuberculous infection throughout all age periods, we find the lowest rates at infancy and they continue to rise as the years advance. The literature and experience on this point are too voluminous and well known to demand specific reference in this discussion.

* Read before American Academy of Tuberculosis Physicians, Atlantic City, N. J., June 8, 1937.

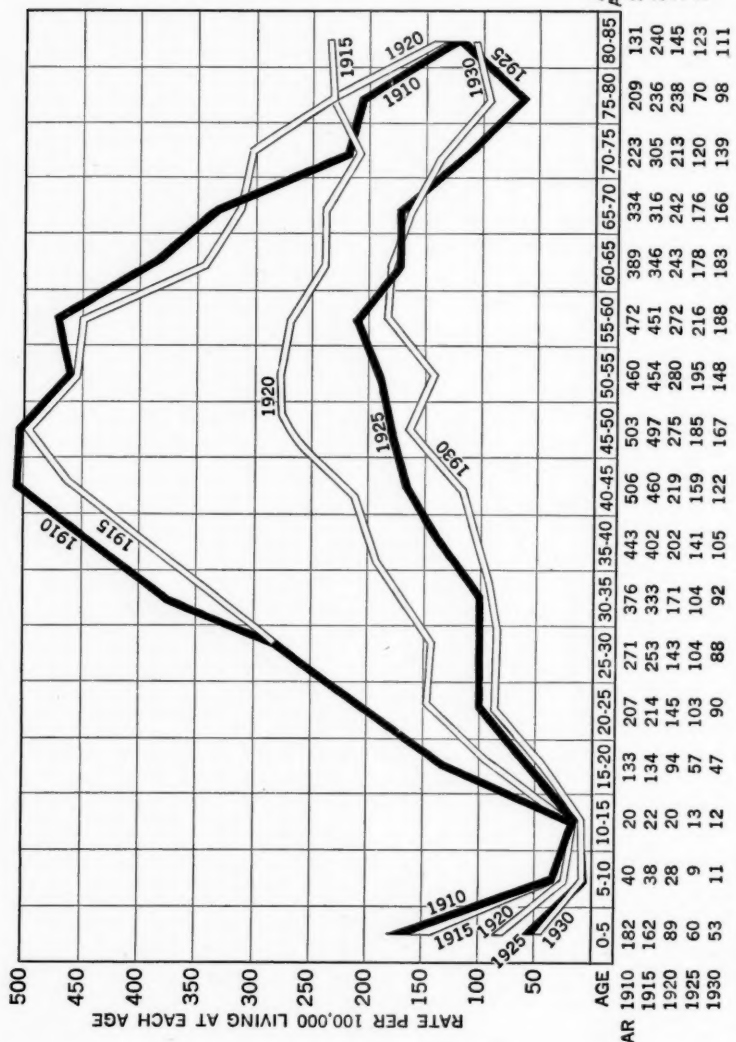
Our knowledge of the pathogenesis of tuberculosis follows closely the same general plan. If the infant survives his third year without succumbing to tuberculosis, in all probability he will not develop a reinfection type until he has reached adolescence, after which



YEAR	AGE 0-5	5-10	10-15	15-20	20-25	25-30	30-35	35-40	40-45	45-50	50-60	60-70	70-80	80-90	ALL AGES
1910	158	47	47	126	182	211	227	215	220	176	139	142	141	61	156
1915	147	43	51	126	178	178	168	184	163	151	132	147	139	74	138
1920	85	24	36	132	165	143	133	119	111	84	92	90	89	45	103
1925	55	13	22	87	112	101	84	78	73	69	61	64	68	32	70
1930	45	6	18	72	92	85	70	56	48	60	46	59	68	56	56

FIG. 1—FEMALE TUBERCULOSIS (ALL FORMS) DEATH RATE by AGE in NEW YORK CITY, 1910, 1915, 1920, 1925, 1930.

time our morbidity curves show a sharp rise which culminates in the peaks described above.



YEAR	AGE 0-5	5-10	10-15	15-20	20-25	25-30	30-35	35-40	40-45	45-50	50-55	55-60	60-65	65-70	70-75	75-80	80-85	ALL AGES
1910	182	40	20	133	207	271	376	443	506	503	460	472	389	334	223	209	131	266
1915	162	38	22	134	214	253	333	402	460	497	454	451	346	316	305	236	240	254
1920	89	28	20	94	145	143	171	202	219	275	280	272	243	242	213	238	145	149
1925	60	9	13	57	103	104	104	141	159	185	195	216	178	176	120	70	123	104
1930	53	11	12	47	90	88	92	105	122	167	148	188	183	166	139	98	111	90

FIG. 2—MALE TUBERCULOSIS (ALL FORMS) DEATH RATE by AGE in NEW YORK CITY, 1910, 1915, 1920, 1925, 1930.

Thus all available data on tuberculosis clearly indicates that it is a disease of adult life. It is during that period that we are confronted with problems of debility and death and the spread of

infection to infants as well as children and adults. It will naturally follow therefore that the greatest achievements in case finding and thereby tuberculosis control must be expected from the adult groups. During the passing years our increased knowledge of the prevalence of tuberculosis has been reflected very definitely in our diagnoses; we are no longer content to accept a diagnosis of chronic bronchitis or bronchial asthma in the aged, for all too frequently it has been such cases that have been responsible for the continued spread of the disease to others.

It has been fairly common practice in most communities to find that from 5 to 20 or more per cent of new cases reported are diagnosed first at or within a month or so of death. It is logical to assume that those cases have been suffering with tuberculosis from 2 to 5 or more years, during which time they have undoubtedly had an opportunity to widely disseminate their disease to others. Because the nature of their illness is unknown their menace to close contacts and associates is all the more important. It is in part from this group that we are continually reaping our annual crop of new cases. It is also the answer for the difficulty encountered in tracing the source case in many new cases diagnosed.

Another cause for our lack of success in early diagnosis is to be found in the fact that by and large we have placed emphasis chiefly on the basis of symptoms. Here again we have abundant evidence to show that in early disease there are as a rule no symptoms, certainly not the classical symptoms of cough, expectoration, blood spitting and loss of weight publicized so frequently. There may be present those less definite symptoms of gastric upset, lack of endurance, fatigue, and so on, but they as a rule do not make sufficient impression on the patient to cause him to seek medical advice. Thus it becomes readily apparent that if we are to find tuberculosis we must direct our efforts to the adult groups, and if we wish to find early disease we must consider some method that will reach such groups in the period before noticeable symptoms have developed.

The logical answer would be a periodic Roentgen ray examination of the entire population. The expense involved in such an approach should not be considered excessive, if we measure our results in lives and community resources saved, for today we have invested many millions of dollars in buildings and equipment to fight tuberculosis, which are costing millions more to maintain, and in the final analysis we are still making rather slow progress in the control of the disease.

It is really not necessary that we should attempt such a wholesale job. Here we have reasonably clear-cut guides. In addition to age and sex incidence we have much data on occupation and economic status of the individual. All of which will assist us in selecting those groups among whom we may expect to find the greatest return.

The mass approach in case finding among apparently healthy individuals is a Roentgen ray job. Fortunately, we have a machine that is well equipped to make large-scale screening operations at a minimum of cost and with a reasonable result. The Powers Rapid Roentgen ray machine has indicated beyond a question of a doubt within the past 5 years that mass action is within our reach. It is well to mention here that this method, or any other similar to it, is but a single step in a well-rounded tuberculosis control program. In any community program the contact case is the most desirable approach and should be the foundation around which these other devices are built.

The first use of this method as a case finding proposition was in New Haven, Conn.,[3a] by the Department of Health, in 1933. That survey was chiefly confined to High and Junior High School students where 6393 persons were Roentgen rayed in $10\frac{1}{2}$ working days, a speed never before accomplished in such work. Our findings clearly indicated the age incidence factor as of the 12 (0.19%) diagnosed tuberculous, 11 were above 16 years. The percentage diagnosed tuberculous by age periods, including about 200 school teachers were as follows:

Age 11 to 15, 3879 examined, 1 (0.03%).
Age 16 to 20, 1461 examined, 6 (0.41%).
Age 21 to 25, 82 examined, 2 (2.44%).
Age 26 to 30, 74 examined, 2 (2.70%).

The incidence of childhood type lesions for the entire group was 6.01%, and it increased steadily with the higher age groups.

Since this case finding survey was completed there have been numerous others by the same method throughout the country; in all, it is estimated approximately at 300,000 persons. A considerable amount of this work has been done among school children. Unfortunately, there has not been a uniformity of interpretation nor have all these results been reported. Some few of these studies however are of the greatest interest because they clearly illustrate the problems herein discussed.

Following the New Haven survey the Connecticut State Department of Health[6] undertook a program to offer the Roentgen ray to school children throughout the state during the winter of 1933 to 1934. This work has never been completely analyzed as to age groups; however it was largely among the grades below High School. There were 56,942 Roentgen ray pictures made. They were interpreted by the medical staffs of the State Sanatoria under rigid checking and therefore may be accepted as closely conforming to the National Tuberculosis Association standards. Of the total, 95.5% were considered negative, only 33 (0.06%) were diagnosed as pulmonary tuberculosis, probably active. There was a total of 1936 (3.4%) referred to the family physician for follow-up, the majority of which (773) was considered only as suspicious. This survey cannot be

said to have been a successful case finding adventure, if we are to consider the costs involved and the cases found. The real value of this program was in its educational stimulus in making the school population, and indirectly the lay populace as well as the medical profession, Roentgen ray conscious. This result may or may not be a valid expenditure of funds. There is a growing body of opinion against the indiscriminate use of our resources charged against hypothetical accounts. We have no proof of the yield in our educational measures, and we can with certainty estimate the cost of case finding measures.

During 1933, Barnard[1] utilized the Paper Roentgen ray method in the study of 18,749 individuals on Home Relief in New York City. This was the first mass survey of such a group that we have recorded, and the findings were most illuminating. For the entire group, 2779 (14.8%) were designated for further investigation. There were 2047 (10.9%) diagnosed as tuberculosis. Of the total, 476 (2.5%) were considered definite, 592 (3.2%) suspects, and 979 (5.2%) as healed. In addition there were detected 732 (3.9%) with obvious cardiac lesions. In the latter group, subsequent follow-up confirmed the Roentgen ray diagnosis and showed a close correlation with luetic infection. The persons Roentgen rayed in this study were comparable only in that they were on relief and that Roentgen rays were offered only to those members of families 10 years or older. Two distinct groups were reached, 10,202 from Harlem where there was a predominance of negroes and Porto Ricans, and 8517 from Red Hook-Gowanus, where there was a predominance of whites. The findings generally in the Harlem group were higher. This emphasized the point previously raised that an intelligent selection of adult groups can be made.

There were three general conclusions in this survey of the greatest moment: 1, a routine survey of apparently healthy individuals revealed 2.5% with pulmonary tuberculosis; 2, if the survey had been confined to those 20 years or over all tuberculosis found below that age would have been discovered in the follow-up of contacts; 3, the classification of disease found indicated that over 70% of the lesions were in a minimal stage.

Barnard reports a per capita cost of $1.78 for the Harlem group, and $1.22 for the Red Hook-Gowanus, where certain improvements in organization methods were introduced.

Downes[2] made a further study of the data on the cases Roentgen rayed in the Red Hook-Gowanus District. She presented the data by age, sex and color for important tuberculosis which tended to show definitely the increase in incidence with increasing years and the characteristic differences between sexes as has been commented on previously in this discussion. She also reported on the follow-up of these cases and contacts in the routine clinic examinations. Of the 272 reëxamined, 196 (72.1%) were classified as minimal, 28

(10.3%) as moderately advanced and 18 (6.6%) as advanced, 9 (3.3%) were undiagnosed and 21 (7.7%) were reversed from the diagnosis on paper. A study of 73 cases classified as suspects on Paper Roentgen ray were later classified as follows: 16 (21.9%) as minimal tuberculosis, 1 (1.4%) as childhood type, 21 (28.8%) were undiagnosed and the remaining 35 (47.9%) as non-tuberculosis.

There were 543 families with 1873 contacts listed for follow-up. For all ages 64.8% were examined, the highest rate being in 54 families where the primary case was advanced or moderately advanced disease in the primary case, and the lowest in 207 families where the primary case was suspicious or non-tuberculous lesions. The new tuberculosis found by these examinations revealed chiefly minimal lesions, the percentage being about equal for all ages in the families with a primary case of minimal, the suspect and non-tuberculous cases. No cases were diagnosed in contacts in families in which the primary case was moderately or advanced disease. This finding was not explained in the report by Miss Downes. Here again the age incidence factor was clearly substantiated, being lowest under 20 years and reaching its peak or about 26 times greater at 50 years and above.

During 1934, the Department of Health inaugurated another survey of this character in lower Manhattan. It involved 25,170 individuals among which we found 824 (3.3%) with manifest pulmonary tuberculosis; of the 824 cases diagnosed, 89.6% were previously unknown. We designated 2900 individuals for follow-up and found 278 (9.6%) with active tuberculosis.

During 1935 and 1936, another survey of a somewhat similar character was conducted at our Meinhard Health Center among Porto Ricans. In this study, we did not use the Powers Rapid Paper Method, instead we utilized an existing radiographic unit and celluloid films, chiefly because of the limitation of space. The persons invited for Roentgen ray were on Home Relief rolls, predominantly of Porto Rican extraction, and limited to those 15 years or older. A complete analysis of these data is under way which will include the costs involved. There were 3214 persons Roentgen rayed and given a routine chest examination on the first visit, 207 (6.4%) were diagnosed as tuberculous. Of the 207 cases diagnosed adult form tuberculosis, 119 (57.5%) were classified as active. The minimal lesions in this survey represented 83% of the total pulmonary cases.

During the current year we have returned to the Harlem area with an enlarged W. P. A. staff to carry on an intensive combing of the entire area. In this area, our population is predominantly negro and Porto Rican, and the death rates are the highest of any area in the City. The negro population in New York City represents about 5% of the total, yet it is responsible for almost 25% of our annual deaths from tuberculosis. Thus far we have

taken approximately 25,000 Roentgen rays with essentially the same results in new tuberculosis, minimal and cardiac lesions as found in the survey by Barnard in 1933. All 3 of the foregoing studies are now being carefully analyzed and will later be reported in detail.

Our experience in this type of mass survey of apparently healthy persons has been most satisfactory and appears to be the best possible approach to the problem now available. The finding of early lesions permits the maximum results in securing arrest at an early date, and further serves to make more economical use of our limited hospital beds. In the Meinhard study, we arranged with 2 of the City Hospitals to reserve about 12 beds for the immediate hospitalization of cases. These beds were used primarily for the early and doubtful cases where intensive bedside study was desirable to determine activity, and for those suitable for pneumothorax. In the latter group, it was possible to induce their collapse promptly after admission, and within a short period discharge them to ambulant care. This method has proven to be of great value, as it is a source of great encouragement to the patient and represents considerable economy in the use of institutional facilities. All cases of advanced disease in need of longer hospital care were immediately placed in other City Hospitals.

Fellows,[4] at the Metropolitan Life Insurance Company, has reported results of the greatest significance. He has utilized the fluoroscope to a greater degree of perfection than most workers in this country. By this method in conjunction with the Roentgen ray and careful physical examination he detected 141 previously unknown cases, of which 65% were classified as minimal. The proportion of minimal cases referred to Mt. McGregor, the Metropolitan Sanatorium, were 5 times as great as the average admissions to other sanatoria. The majority of these patients were detected at a time before they had toxic symptoms. The close affiliation with Mt. McGregor resulted in prompt hospitalization and a more rapid arrest of the disease. His experiences clearly indicates what may be done successfully in a large business organization.

Colonel Pillsbury,[7] at Camp Dix, New Jersey, routinely Roentgen rayed 7405 C. C. C. men, predominantly white and under 30 years. Seventy (0.94%) were classified as active, 76 (1%) were questionably active tuberculous, and 376 (5%) were tuberculous with no activity. Thus he found a total of 522 (7%) with tuberculous lesions of the adult type. The lesions adjudged non-active on this examination, considering the age of the men, should nevertheless be considered as potentially active. His percentages of disease in the groups over 35 years were in each instance higher than in those under 30 years. If these findings are at all indicative of what might be expected among all enrollees' in the C. C. C. Camp throughout the country, it may be readily concluded that a similar program should be a part of the Government's responsibility in their administration.

From the standpoint of Government responsibility we should naturally consider the Army, Navy and Marines as well as Civil Service and other employees. If such a device had been available in 1917 at the time of the Draft, the taxpayer today could easily have been relieved of hundreds of millions of expenditure in compensation and hospital costs.

After a careful perusal of the volume of material in the current literature on tuberculosis surveys, it becomes immediately obvious that the great bulk of our effort in the past has been devoted to contact examinations. This is fundamental in any tuberculosis program. The problem among this group that is presented time and again is that as a rule we only examine about half of the known contacts, and that the percentage is highest among the younger ages where we do not expect to find manifest tuberculosis. The adult ages are the most important and demand greater effort to secure coöperation. A study of mortality and morbidity by age groups clearly indicates these facts.

We have always devoted a greater amount of effort to the child rather than the adult. Partly because of the greater ease with which they can be reached and partly because there has been a general feeling that if the early manifestations of tuberculosis could be detected there we could prevent later serious disease in adult life. Since 1920 there has been numbers of extensive surveys among apparently healthy children to determine the incidence of infection and disease. These studies have shown in general an increasing frequency of both as the age periods advance. The incidence of pulmonary tuberculosis has been lower than the childhood types. The yield of pulmonary lesions has been so small that such methods may well be considered excessively costly as case finding methods. The importance of the childhood type lesion is still a debatable issue. If we accept the theory that such lesions are a potential menace then our attitude should be to develop a definite program for their detection and later supervision. On this point there is some information of interest, but much more is required before we can accept it as a sound procedure.

Stewart[9] reports, from his experience at Lymanhurst in the supervision of 10,000 children, that in only 0.04% had he observed a progression from a childhood to an adult type.

Pope,[8] reporting on 5000 children followed in the Massachusetts clinics, stated that the progression from childhood to adult type is 0.93%.

Hall and Chang[5] reported on 1007 Chinese of the professional class. Of 144 originally classified as trachea-bronchial tuberculous lymphadenitis, 6 (4.2%) developed manifest pulmonary tuberculosis in an average of 54.5 months.

Edwards[3b] reported on 155 individuals with a diagnosis of childhood type from the New Haven Dispensary. In 9 (5.8%) there had been noted a progression to adult pulmonary tuberculosis within

an average period of 242.7 days, all of which occurred during late adolescence.

These reports are significant but require substantially more volume before we can definitely state that the detection of childhood type lesions is a productive source of later adult lesions.

A comparison of our mass studies among apparently healthy children and adults clearly indicates that the latter group is the most productive in significant tuberculosis, or the type that is or will become debilitating and a community problem. It is firmly believed that we have reached the time when we should definitely shift our emphasis from the child to the adult. This shift need not be made blindly as we have a considerable volume of facts and data that clearly indicates the broad general paths that we should follow. From the standpoint of age, 15 years is the lower level, as to sex, our emphasis in females should be greatest between 15 and 30 years, after which we should continue with a consistent drive. In the case of males we again begin at 15 years but find our peak between 50 and 60. From the economic factor we can expect a higher yield in the low income groups and from the tenement house districts. Racially, the colored groups will show higher percentages than the whites in about the same age periods and economic divisions. From the occupational standpoint our course has been clearly defined by Whitney[10] in her analysis of death rates by occupations on the basis of data of the U. S. Census Bureau, 1930. If the tuberculosis administrator will carefully evaluate these various factors in his community it is believed he can intelligently proceed to formulate a sound case-finding program that will be productive in its results and at a cost commensurate with the funds invested.

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DIAGNOSTIC IMPORTANCE OF THE TONGUE IN INTERNAL MEDICINE.*

By Bernard I. Comroe, M.D.,

INSTRUCTOR IN MEDICINE, SCHOOLS OF MEDICINE AND DENTISTRY, UNIVERSITY OF PENNSYLVANIA, PHILADELPHIA, PA.

Examine the Tongue! Were the tongue carefully inspected in every patient reporting to the physician or dentist, important diag-

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nostic pointers would frequently be found. Too many clinicians merely order "Stick out your tongue" and 10 seconds later have no idea what they have seen. They have looked but have not seen. In the Chinese language, there are 2 words, one meaning "to look," the other, "to look see;" it is this ability "to look see" which should be developed by physicians.

There are practitioners who unfortunately resort too much to the laboratory method of diagnosis. Examination of the tongue and palpation of the pulse have fallen by the wayside with many young physicians. Gastro-intestinal Roentgen rays, gastric and duodenal analysis, electrocardiographs, orthodiagrams, and the like are often needlessly requested before a thorough history and physical examination of the patient have been completed. This is true, to a lesser extent perhaps, in our hospital wards and outpatient departments. An overzealous but misguided interne, in a mistaken effort to prove his skill before the chief, will drive a tired, weakened patient through the gamut of special tests in the shortest possible time to have the diagnosis the following morning for ward rounds. He may ignore important leads in diagnosis presented by such simple manoeuvers as examination of the scalp and skull for possible metastatic lesions, inspection of the tongue, finger nails, umbilicus, and anus, and palpation of the pulse.

Hippocrates described the tongue as it appears in numerous diseases. Careful routine inspection of this organ reveals manifestations of many systemic diseases. Among these are the chancre, mucous patch, or gumma of syphilis; the strawberry tongue of scarlet fever; the smooth glossy appearance in pernicious anemia and sprue; the pigmentation in Addison's disease; the pallor in severe anemias; the cyanosis in congestive heart failure, congenital heart disease, and polycythemia; the dryness in diabetes mellitus, fevers, mouth breathers, and dehydration; the recurrent canker sores in allergic individuals; the ulcerations of acute leukemia and agranulocytic angina (pernicious leukopenia);[3,7] the characteristic lesions encountered in drug sensitivity or poisoning; the glossitis of severe anemias of pregnancy, dysentery, simple achlorhydric anemia, and Plummer-Vinson syndrome; the yellow pigmentation most evident along the margins in obstructive jaundice; the tremors of paralysis agitans and hyperthyroidism; the sharp, quick, jerky movements of the tongue in chorea; the scars of epilepsy; these are examples of the importance of the tongue for internal medicine.

The lymph drainage from the tongue is chiefly to the submaxillary and upper and lower deep cervical nodes; the submaxillary nodes receive drainage from the anterior two-thirds of the tongue; the deep cervical nodes, from the posterior third. The motor nerve supply of the tongue is from the twelfth nerve. Since the nucleus of this nerve lies well below that of the facial nerve (seventh),

paralysis of the tongue may occur on the side opposite to that of a concomitant facial palsy. In paralysis of one side of the tongue, this organ when protruded deviates toward the paralyzed side pushed by the non-affected muscles on the healthy side. Ignorance of this relation has led to faulty neurologic diagnosis.

Common sensation for the anterior two-thirds of the tongue is excited through the lingual branch of the fifth nerve, whereas the glossopharyngeal nerve excites common sensation and taste for the posterior third. The sensation of taste for the anterior third is stimulated through the chorda tympani. In diseases involving the epiglottis, one not infrequently encounters reflex cough or hiccough; this has an anatomic basis, for the epiglottis as well as a small area of the tongue anterior to it is supplied by the internal laryngeal branch of the superior laryngeal nerve.

To evaluate the abnormal tongue, familiarity with the tongue is indispensable, noting particularly color, fur, pallor, papillæ, evidence of inflammatory changes, blood-vessels on the under surface, form, size, movement and humidity. Most textbooks of medicine today devote little space to this organ. The diseases they describe usually include acute, chronic, and Möeller's glossitis, black tongue, leukoplakia, syphilis, tuberculosis, mycoses, and tumors.[16] The tongue may be narrow and pointed at the tip or large and flabby with a thick and rounded tip and with margins marked by the teeth. In nervous individuals, the tongue is quickly protruded and quickly withdrawn. In the phlegmatic, its motions are sluggish. In old age, the tongue is usually coated and less moist than in younger individuals and becomes dry and even glazed at the onset of the slightest ailment. This is of importance lest we regard as serious that which is only a trivial disorder.[4]

Alterations in the appearance of the tongue are commonly related by the lay mind, as well as by many physicians, to disorders of the gastro-intestinal tract. It has been regarded as the mirror of the stomach.[19] Lewis[14] says: "red raw tongue, red raw gut." The time was not far distant when a white tongue was looked upon as a sure sign that the stomach was out of order and that a dose of calomel was indicated.[5] Many persons have a coated tongue in health, especially smokers.[4]

The coated tongue is the abnormality most frequently encountered. The so-called fur of the tongue is thickened epithelium covering the filiform papillæ plus various bacteria. The filiform papillæ are the most numerous and smallest of the papillæ. Each is a conical projection, sometimes ending in fringes of hairlike processes. The epithelium covering these is constantly shed and worn away and as constantly replaced.[8]

Fitzwilliams[8] has divided the process of furring of the tongue into several stages: the dotted or stippled tongue, the coated or loaded

tongue, the white strawberry tongue, the furry or shaggy tongue, and the typhoid, dry, brown, crusted tongue. The dotted tongue often occurs with the slightest gastric upset or dietary indiscretion. The strawberry tongue is characteristic of the early stages of scarlet fever, but is also seen in many acute infections, including acute bronchitis, typhoid fever, pneumonia, etc. A diagnosis of scarlet fever should never be made on the appearance of the tongue alone. A coated tongue is frequently seen in association with emotional disturbances in the patient. In intestinal disturbances not complicated by a deranged stomach or dehydration, there is no characteristic change in the tongue; but habitual constipation is often associated with a large, furred tongue. The tongue may be furry in areas which are temporarily out of use, as around chronic ulcers when pain immobilizes this part. A crusted, brown tongue is frequently encountered in intestinal obstruction, peritonitis, terminal cardiac failure or malignancy, etc.

A red, bare or smooth appearance of the tongue may be associated with long standing chronic disorders such as empyema, dysentery, diabetes, tuberculosis, etc. The wearing of an upper plate over long periods of time occasionally produces a smooth, polished, bright red tongue, without pain or inconvenience. Although in many acute disorders of the gastro-intestinal tract the tongue tends to become furred, in acute gastritis it is frequently red, especially at the tip and edges. In acute peritonitis, the tongue is usually small, red, and tender, with little fur and is usually dry.

In carcinoma of the stomach, the tongue may be clean and appear healthy if there be no associated febrile reaction. Schwindt[20] has found in many cases of gastric or duodenal ulcer a peculiar change in the tongue manifested as multiple, round or oval, confluent epithelial defects, which disappeared on healing of the ulcers. These looked like superficial ulcers, were not sensitive, and were frequently symmetrical; they were approximately 2 to 8 mm. in size; the edges were smooth. He saw them occasionally with carcinoma of the stomach. In most instances, these lesions were chiefly on the posterior part of the tongue, in the middle, anterior to the large papillæ; occasionally they were unilateral.

Fenwick[6] noted a definite smell from the tongue itself (not from the breath) with abdominal sepsis. This may be the smell characteristic of pus or rather a fecal odor, sickening to the observer. He has postulated that the tongue may give the first indication of the extremely rapid absorption (in this case of toxic material) from the peritoneum. This smell from the tongue remained even after gargling and washing the mouth. In these cases the tongue usually was not covered by fur, but was dry and beefy.

Discolorations of the tongue may be significant or may be derived from the foodstuffs. Significant changes occur in Addison's disease,

xanthelasma and ecchymoses (as from injury, purpura, or scurvy). In Addison's disease, in addition to the pigmentation elsewhere in the body, there are often bluish-black smears on the mucous membrane of the lips, cheeks and tongue, as if a pen had been wiped upon them. Stains from fruits, acids and alkalis, metals, chocolate, tobacco, nuts, prunes, licorice, etc., may discolor the tongue. The bluish discoloration of the tongue produced by grape juice persists for several hours and can be misleading.

Binkowitz[2] described in relation to the tongue an early sign of cardiac decompensation. If the tongue is protruded from the mouth and is held in a pendant position for at least a minute, the normal red color gives way to a blue or cyanotic hue, or in severe cases becomes almost black. If the patient elevates the tongue to the back of the upper incisors without exerting pressure a marked distention of the ranine veins occurs, which Binkowitz believes is an early sign of circulatory failure.

Glossitis with atrophy of the lingual papillæ is a common manifestation in pernicious anemia, achlorhydric anemia, the anemia of pregnancy,[13] pellagra, sprue, Plummer-Vinson syndrome,[17,21–23] malnutrition attended by dysentery and anemia,[11] intestinal stricture, pyloroplasty complicated by peritonitis, dibothriocephalus latus infestation[10] and achlorhydria.[15] Middleton showed that rats placed on a low vitamin B diet present a smooth bald tongue with marked papillary atrophy. He inferred that in most cases an atrophic tongue is dependent on vitamin B deficiency. The completely bald tongue associated with pernicious anemia can exhibit return of papillary markings with liver treatment.

Middleton[19] made tongue prints on smoked paper. His conclusions were as follows: Patients with hyperchlorhydria rarely have smooth tongues, but often scrotal or coated tongues. In organic non-malignant disease of the gastro-intestinal tract there is a tendency to the coated and scrotal types of tongue. This is more marked when hyperchlorhydria coexists and is apparently proportional to the degree of the hyperacidity. Peptic ulcer shows the most evident tendency in this direction, with chronic colitis and chronic cholecystitis following in order. When there is achlorhydria, smoothing of the tongue is common. Functional conditions are rarely attended by smoothing of the tongue. Neither normal nor coated tongues are commonly associated with anemia.

Urticaria may occur locally on the tongue. One such allergic patient could never eat fish without a crop of blisters developing on his tongue.[8] Lindsay[15] describes a patient in whom canker sores came regularly on the tongue within 24 to 48 hours after eating even the smallest amount of English walnuts. Great swelling of the tongue may develop on an allergic basis; the tongue may also become edematous as a consequence of any inflammatory condition

within the mouth, arising either from a general condition as in mercurial stomatitis, or from local disorder as in ulceration of the gum around a tooth with an infected socket.[1]

Among the many causes of "burning tongue" as well as of small ulcerations on this organ is an electrogalvanic burn caused by dentures composed of 2 metals constituting a galvanic battery, the saliva acting as an electrolyte. Lain[12] has pointed out that such galvanic currents may be set up in the mouth generated by 2 metals used in dental fillings, crowns, and bridgework.[9]

An uncommon abnormality of the tongue is the occurrence of a lingual thyroid. In this condition for some unknown reason the anlage of the thyroid gland, which arises in the region of the base of the tongue, fails to migrate or migrates incompletely; 144 proven cases of this condition has been recorded.[18] The symptoms are not characteristic, and arise merely from pressure in this region, resulting in dysphagia, dysphonia and dyspnea. The lesions are usually small, round, hemispherical masses protruding into the pharyngeal fossa. Removal of these masses may produce hypothyroidism. They frequently respond to iodine and thyroid medication.

Other lingual manifestations of systemic disease include uremic stomatitis, disturbances associated with blood dyscrasias, drug eruptions, mycotic infections, neurologic disorders, etc. These will be made the subject of a later report.

Summary. 1. A plea is made for adequate inspection of the tongue of all patients.

2. Some common lingual manifestations of systemic diseases are described.

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LOSS OF BODY HEAT AND DISEASE.

By Walter Landauer, Ph.D.,
PROFESSOR OF GENETICS, CONNECTICUT STATE COLLEGE, STORRS, CONN.

(Storrs Agricultural Experiment Station.)

With regard to infectious diseases it is well recognized that the hereditary constitution plays an important rôle in determining whether or not an individual will resist exposure to particular kinds of microörganisms. There are mutations which, apparently in a specific way, confer immunity against particular infections, though the nature of these genetic protective mechanisms is unknown. There are also hereditary traits in body build which affect the chances that an individual will contract certain infections, such as pulmonary tuberculosis. But with regard to organic disease the tendency still prevails to believe in the existence of clear-cut distinctions between hereditary ailments, making their appearance earlier or later in life, and pathologic changes due to influences of the external or internal environment. From experimental studies, however, it is becoming ever clearer that sharp division lines here also do not exist. This is true even for congenital abnormalities. Thus, the incidence of polydactyly in guinea pigs, in addition to its dependence upon the presence of certain genes, appears to be influenced by external agencies acting upon embryonic growth, by litter size, by weight and age of the mother, and probably by still other factors.[20] Or, the frequency of appearance of harelip and cleft palate in mice, in addition to genetic factors, has been found to depend upon sex of the individual, litter size, age of the mother, and probably numerous other agencies.[17] There are many instances of a similar nature. This evidence indicates that the actual expression of a trait is likely to be the result of complex interactions. Such interactions may take place (*a*) between the major genetic determiners of a trait and one or many other genes (genetic environment or residual heredity); (*b*) between the genes or gene controlled events and physiologic processes within the organism or, before birth, within the mother's body (internal environment); and (*c*) between hereditary factors or genetically determined structures or functions and the surroundings of the developing or fully formed organism (external environment). Multiple, simultaneous or successive, interrelationships provide an unlimited source of variation. Only a detailed analysis of such interdependence can give a real insight into the etiology of pathologic phenomena.

It is likely that the genesis of many disturbances of structure and function involves a chain of events, with the more important links represented by interactions between the external environment and the organism or its parts, and by internal readjustments in response to changes in particular parts or organs. Observations which illus-

trate relationships of this type have come to light through studies with so-called Frizzle fowl and a short account of this work may serve to call attention to the necessity for clinical observations of a similar nature.

Our work with Frizzle chickens was started with the intention of ascertaining the manner of inheritance of the plumage traits to which this breed owes its name. The characteristic features of the plumage of Frizzle fowl are curling and brittleness of the feathers, and the latter by abrasion frequently leads to more or less complete bareness of the body. It was soon found that these peculiarities are determined by a single gene with incomplete dominance over the normal plumage condition.[12] At the same time it was realized, however, that Frizzle chickens differ in many ways from normal fowl. There is great variability in all of the abnormal traits, but the following features are generally present. The basal metabolism is much increased. At an external temperature of 28° C. (82° F.) the metabolism of Frizzle chickens is above that of normals. Within the range of 28° to 17° C. no changes occur in the metabolic level of normal fowl, but in Frizzle chickens the metabolism increases by about 4% for each degree of reduction in the environmental temperature, and at 17° C. (50° F.) the metabolism of Frizzle chickens exceeds that of normal ones by already more than 100%[1]; it continues to rise with falling external temperature. The heart rate of Frizzle fowl is much increased (adult average at room temperature is 27% above normal in females and 68% above normal in males) and is markedly labile.[2a] There is frequently a distinct sinus irregularity, and sometimes more serious injury to the heart, for example, heart block.[3] The heart itself shows conspicuous hypertrophy of both ventricles,[2b] and this hypertrophy tends to become more pronounced with age.[13] The amount of circulating blood is definitely increased, especially in mature Frizzle fowl.[13] There are also changes in the cellular composition of the blood. In Frizzles which live in a relatively favorable external environment the number of red cells and the relative frequency of the different types of white cells are much more variable than in normal chickens, though the averages do not differ significantly. If conditions are less favorable (for instance, low external temperature), we find a definite relative lymphocytosis and leukopenia and subnormal hemoglobin values. The relatively frequent occurrence of immature red cells in the circulating blood of Frizzle chickens indicates more rapid destruction and replacement than is normal.[11a] The spleen is enlarged. The food intake of Frizzle chickens generally is greater than normal, and, presumably as a direct consequence of this, it is found that the crop, the gizzard, the pancreas, and the kidneys are larger than normal. Length and especially capacity of different parts of the intestinal canal also exceed that of normal fowl. Young Frizzle chickens show a conspicuous lack in body fat, while adult Frizzles

frequently have excessive fat deposits. Water vaporization is reduced to about half the normal amount. Between hatching and the age of sexual maturity the mortality of Frizzle chicks is much greater than normal. Sexual maturity generally is delayed, and may be suppressed entirely if conditions are unfavorable. Size and structure of the sex glands vary greatly. The ovaries tend to be much smaller than normal. The testes of young Frizzle males frequently are considerably larger than normal and show signs of increased sperm production and of exhaustion of the tubules; in sterile Frizzle males past the normal age of sexual maturity the testes generally are very small. It is of interest also that the eggs of Frizzle hens, irrespective of their mates, show reduced hatchability (increased embryonic mortality). Among the glands of internal secretion the thyroids and adrenals are strikingly abnormal. The adrenals as a whole are large in proportion to body weight[13] and the amount of medullary tissue is increased in comparison with the cortex.[10] Size and structure of the thyroids of Frizzle chickens vary with the conditions of the external environment, ranging from exhaustion atrophy (low external temperature) to hypertrophy and hyperplasia (more favorable environmental temperature) and to normal structure but increased size (protection from low temperature plus high-fat diet).

It seems likely that the organism of Frizzle chickens in many other ways differs structurally and functionally from that of normal fowl. However, let us turn to the question of etiology. How does this complex syndrome arise? The majority of symptoms vary in extent and severity with external conditions. This has been established for basal metabolism, food consumption, disturbances of circulation and of reproduction, and for the findings in the glands of internal secretion. The one constant feature is presented by the plumage changes. The frizzled condition of the feathers is determined within the feather follicles. This is shown not only by the lack of influence of variations in the external environment upon the plumage; but, if a piece of skin of a newly hatched Frizzle chick is transplanted onto a normal feathered host, the transplant will develop typically frizzled feathers in spite of its normal organic surroundings.[10] This suggests strongly that the plumage peculiarities of Frizzle fowl are the only trait under immediate gene control, while the other changes are links in a chain of secondary alterations. We shall refer below to further proof for this conclusion.

The curliness of the feathers unquestionably reduces greatly the heat insulating value of the plumage of Frizzle fowl. This loss of protection becomes exaggerated with abrasion of the feathers and bareness of the body. Hence, it is found that the temperature differential between body and surrounding air is much greater in Frizzle than in normal fowl, and it is not surprising that in a cold environment the body temperature of Frizzle chickens tends to fall below

the normal level. Such symptoms of exposure have been produced in normal feathered chickens by removal of part of the plumage and keeping the birds in a cold environment.[5,9b]

The abnormalities of Frizzle chickens in many ways bear a striking resemblance to the symptoms of Graves' disease or of experimental hyperthyroidism. Such parallel phenomena concern acceleration of metabolism and of heart rate, hypertrophy of the heart, increase in blood volume, lymphocytosis and leukopenia, reduced hemoglobin, histologic structure of the thyroid, temperature lability, and so on. Even the increased temperature differential between the body surface of Frizzle fowl and the surrounding air has its parallel in frequent increases of the skin temperature in humans suffering from Graves' disease.[14] Are Frizzle chickens, then, in a condition of hyperthyroidism? The fact that water vaporization is reduced, the opposite of what generally happens in hyperthyroidism, already raises some doubts in this respect. Experiments which were designed to test this question revealed that environmental conditions must be taken into account. Various physiologic tests demonstrate that at low external temperature, with basal metabolism at peak values, Frizzle chickens are subnormal with regard to the amounts of circulating thyroid hormone. This is shown by the following facts. Greater than normal amounts of desiccated thyroid must be administered to Frizzle chickens in order to produce molting (the typical sign of hyperthyroidism in fowl) and loss of body weight.[1] The Reid Hunt test is negative.[11b] Subnormal body temperature will become normal when thyroid hormone is supplied.[9a] In view of all available observations, this can mean only that, in spite of increased thyroid activity (as evidenced by the histologic structure of the gland), the body is not supplied with sufficient amounts of hormone to satisfy the demands created by the accelerated metabolic rate. On the other hand, if Frizzle chickens are suddenly transferred from cold to warm surroundings, it is found that they pass through a short period of hyperthyroidism (increase of body temperature; positive Reid Hunt test; disturbances of feather pigmentation, etc.). If Frizzle chickens remain permanently at very high temperature, they appear to be physiologically normal.

Frizzle fowl show the most extreme abnormalities when they are brought up in a relatively cold environment. Since under such conditions these birds have less thyroid hormone circulating in their body than normal chickens, their abnormalities must be due directly to heat loss, sympathetic overstimulation and increased metabolic rate. This is interesting with regard to such features as the hypertrophy of the heart. In the case of Graves' disease it has been contended by some that the hypertrophy of the heart is preceded by myocardial damage and by specific effects of the thyroid hormone upon the heart muscle,[7] while others assumed that the hypertrophy

is simply the result of increased work. Our observations on Frizzle fowl clearly favor the latter alternative, *i. e.*, overwork, since hyperthyroidism is excluded as a possible cause and other direct effects on the heart tissue appear unlikely. If, in addition to increased work, excitatory effects play a rôle in the heart hypertrophy, they must be assumed to originate from increased metabolism or peripheral sources (heat loss in Frizzles) rather than from the thyroid.

The outstanding rôle which environmental temperature plays with regard to all our observations on Frizzle fowl is explained by its importance in relation to loss of body heat. The greater is the heat loss, the higher is the basal metabolism. Other adaptations and readjustments follow. But under extreme conditions (that is, extreme for Frizzle fowl) various organs, *e. g.*, the heart or the thyroid, may reach their limits of adaptability, with consequent exhaustion and structural break-down or functional disturbances, leading to death. If heat loss stops suddenly (transfer to heated quarters), less thyroid hormone is needed for metabolic activity, but since the thyroid gland needs some time to adjust itself by reducing its output to the new physiologic level, there ensues a short period of oversupply of hormone with consequent symptoms of hyperthyroidism. *Mutatis mutandis*, the same may be assumed to hold with regard to the adrenals.

Direct proof for the correctness of this interpretation was obtained when the regulation of body temperature of Frizzle fowl was compared with that of normal chickens from which a large part of the plumage had been removed.[96] Both types of birds showed exactly the same reactions. In a cold environment their body temperature was somewhat below the normal level. At low external temperature the injection of adrenalin or ephedrine caused an abrupt decline of body temperature and death in Frizzle and partly deplumed normal chickens, while only a slight effect was observed in the control animals. In a warm environment, on the other hand, similar treatment produced little effect in Frizzle and partly deplumed normal chickens, while in the controls it caused hyperthermia and death. Ergotamin gave similar results. These observations show that typical symptoms of Frizzle fowl can be duplicated by removing a part of the body insulation from normal chickens, thereby exposing them to excessive loss of body heat. The results suggest also that the sympathetic nervous system acts as a transmitter of the stimulation caused by the abnormal heat loss and the accelerated metabolism. In rats it has also been shown recently that the effects of thyroid hormone administration vary with the environmental temperature; in fact, within a certain temperature range (and for a uniform dosage) it was found that the relation of external temperature to survival period of the animals was approximately linear.[4]

If Frizzle fowl had been studied without regard to their "clothing"

and without consideration of the conditions of their living quarters, their abnormalities almost certainly would have been diagnosed as due to endocrine disturbances. This leads one to wonder if scanty body protection and lack of proper heating or other climatic factors do not play a much greater rôle in the etiology of human disease than is realized at present. For Frizzle fowl we are certainly justified in saying that with regard to structure and function their bodies are "resonators" of their environment. We have no reason to doubt that the scanty feathering of Frizzle chickens only exaggerates a situation which exists in normal fowl. Does not this evidence suggest that there is truth in Petersen's claim[16] that humans are "cosmic resonators," and that cosmic changes are likely to be reflected in manifold ways by the human organism? These problems deserve intensive study.

Among human diseases it was pointed out by Mills[15a,b] that the incidence and severity of exophthalmic goiter, diabetes and pernicious anemia appear to be related to storm frequency and temperature variability. More or less convincing evidence of a similar nature was put forward by Petersen for many other pathologic phenomena.[16] A condition which probably has much in common with the findings in Frizzle fowl is the "glycosuria of vagrants" reported by Hoppe-Seyler.[6] This author observed glycosuria of short duration, together with circulatory and digestive disturbances, as a consequence of an irregular and poorly balanced diet if linked with physical exertion and exposure to inclement weather. In general, the rôle which exposure to low external temperature plays in human metabolism[15,16,18] essentially is the same as was observed in Frizzle fowl and may be assumed to lead to similar consequences.

Exposure to cold is recognized as a partial cause in paroxysmal hemoglobinuria, Thomsen's disease and Raynaud's disease.[19] While in these cases low temperature only precipitates the symptoms which have their real cause in internal abnormalities, they demonstrate that an organism which functions normally at one external temperture, may show serious disturbances at another. There are further similarities, however, between these conditions and the situation in Frizzle fowl. In Raynaud's disease, for instance, abnormalities of the sympathetic nervous system apparently lead to endocrine and metabolic disturbances similar to those produced in Frizzle chickens by sympathetic overstimulation. These endocrine and metabolic abnormalities in both cases are symptoms rather than causative agencies. Evidence is accumulating that the same holds true in other diseases, even in the case of such a classical "thyroid" disturbance as Graves' disease.

Decision of what is cause and what effect is frequently made difficult on account of reciprocal relationships. Thus, increased secretion of thyroid hormone accelerates metabolism but acceleration of metabolism (for instance, by lowering of external tempera-

ture) also stimulates secretion of thyroid hormone. Similar reciprocal relations exist between thyroid and adrenal[8] and probably in still other cases where the autonomic nervous system acts as an intermediary.

Our observations on Frizzle chickens also emphasize the conclusion that the histologic picture of increased activity of the thyroid gland or, in fact, the demonstration that the thyroids produce more hormone than normal does not necessarily indicate that the organism as a whole is in a condition of hyperthyroidism. The opposite, *i. e.*, hypothyroidism, may be, and in the case of Frizzle chickens actually is found. This will always occur when the demands of the body for thyroid hormone on account of increased metabolism, adrenal insufficiency or for other reasons exceed the capacity of the thyroids for hormone production.

The complexity of events produced by the Frizzle mutation is interesting in still other respects. We have seen that all the different changes represent a series of adjustments to a single primary factor, namely, increased loss of body heat. The plumage abnormality which accounts for the excessive heat loss may in turn trace back to a metabolic disturbance. Histologic study of the feather follicles has so far produced little evidence for structural abnormalities in feather formation, and it seems likely that the frizzling is due to disturbances in keratin metabolism. In many other instances where changes in several organs or functions are found, we may similarly be dealing with complex adaptations and readjustments rather than with multiple disease symptoms *sensu stricto*. Organisms are delicately balanced. Changes in one function necessitate adjustments in other functions. If an organism is unable to make such adjustments, it will perish. This unquestionably happens in many Frizzle chicks (increased mortality between hatching and maturity), and the same may be assumed to occur in other instances of complex syndromes. The immediate cause of death may be only failure of adjustment or of compensation in one organ to alterations in the functioning of another organ. Latitude of adaptability of various organs rather than their perfect adjustment for one "normal" level of activity will frequently hold the balance of life and death. Among Frizzle chickens, for instance, those which from birth on have larger and better functioning thyroids, undoubtedly will have a greater chance to survive, and it has actually been found that, apparently due to natural selection, the thyroids of Frizzle chicks at hatching are larger than those of other breeds of fowl and show increased activity.[10] Yet, frequently they cannot keep pace with the demands of the body. In some other respects the adjustments of Frizzle chickens appear to be more successful.

On the whole, the evidence from Frizzle fowl demonstrates impressively the inseparableness of organism and environment. As function and structure are only aspects of one entity, so is each

organism in multiple ways an expression of its particular environment. It seems certain that this applies to humans also. But in our society the effects of the natural environment are likely to be complicated by social factors which are another real and integral part of our existence. The fact, however, that the human environment is more complex than that of lower animals does not make it less likely that our bodies reflect its forces.

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THE CALCIUM ION CONCENTRATION OF THE SERUM IN ALLERGIC DISEASES.*

By William B. Sherman, M.D.,
clinical assistant, department of allergy, roosevelt hospital, new york city,
and
Mary Glidden, A.B.,
assistant chemist, department of allergy, roosevelt hospital, new york city.

(From the Department of Allergy of the Roosevelt Hospital, Dr. Robert A. Cooke, Director.)

The belief that calcium may be a factor in allergy is based on the studies of the physiologic effects of inorganic salts by Ringer, Howell and others,[1] which showed that calcium salts lessened the permeability of membranes and depressed smooth muscle. Since transudation of serum and smooth muscle spasm play important

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parts in allergic phenomena, calcium compounds have frequently been advised as therapeutic agents in these diseases.[12]

Some writers have found an actual calcium deficiency associated with allergic conditions, but the results of various authorities are quite contradictory. Novak and Hollander,[11] Brown and Hunter,[2] and Sterling[17] have reported that the serum calcium is low in allergic diseases. On the other hand, Schwartz and Levin,[15] Criep and McElroy,[5] Ramirez,[13] Kern and Teller[9] reported normal figures, while Schamberg and Brown,[14] Sonnenschein and Pearlman,[16] Greenbaum[7] and Drilhon[6] all found values higher than normal. The discrepancies may in some cases be due to choice of the normal range, but it is obviously impossible to reconcile all these opinions.

Furthermore, it is important to consider the state of chemical combination of the calcium in the serum, which was poorly understood when most of these papers were written. It is now known that a part of the calcium is freely diffusible through semipermeable membranes, while the remainder is bound to the serum protein and is not diffusible. There is some difference of opinion as to the subdivision of the diffusible fraction, but probably most of it is present as simple calcium ions, while a small portion is combined with citrate and other complex anions.

Only the ionized portion of the calcium is physiologically active. Variations in the non-diffusible portion, which accompany differences in the serum proteins, do not cause the characteristic symptoms associated with changes in the serum calcium. Several methods have been suggested for determining the diffusible calcium: (1) by dialysis or ultrafiltration through suitable membranes; (2) by considering the cerebrospinal fluid a protein-free filtrate of the plasma; (3) by electrometric measurements with a calcium electrode.

Greenberg and Gunther[8] applied the ultrafiltration method to the sera of 14 allergic patients and found the diffusible calcium to be normal in all but one case. Cantarow[4] by analyzing the spinal fluid of allergic individuals found an increase of the filtrable fraction with a normal total serum calcium. Brown and Ramsdell,[3] in experimental anaphylaxis, found the diffusible calcium definitely elevated. However, none of these methods of fractionating the calcium has proved really practical or accurate.

During the past few years, McLean and Hastings[10] have developed an entirely different method which gives promise of greatly advancing knowledge of this matter. Variations of the calcium ion in fluids perfused through an isolated frog heart produce characteristic effects on the contractility. By this means it is possible to measure quite accurately the amount of ionized calcium in serum or other suitable fluids. Furthermore, they were able to show that the calcium ion concentration so determined bore a mathematical relationship to the total serum calcium and the serum protein, as measured by ordinary analytical methods. Therefore, by carrying

out these two chemical procedures and applying their formula or diagram, it is possible to calculate the ionized calcium without resorting to the complicated physiologic method.

Method. This method of study was applied to the sera of 53 patients with various allergic diseases, and 25 control observations were made upon relatively normal subjects. Both groups were free of other diseases known to affect calcium or nitrogen metabolism. Blood for analysis was drawn by means of a tourniquet, but prolonged stasis was avoided. In a preliminary study, it was found that the error introduced by careful use of the tourniquet was relatively small, approximately —.04 mg. of ionized calcium per 100 cc., and since it affected the normal and allergic figures equally, this method was suitable for practical use.

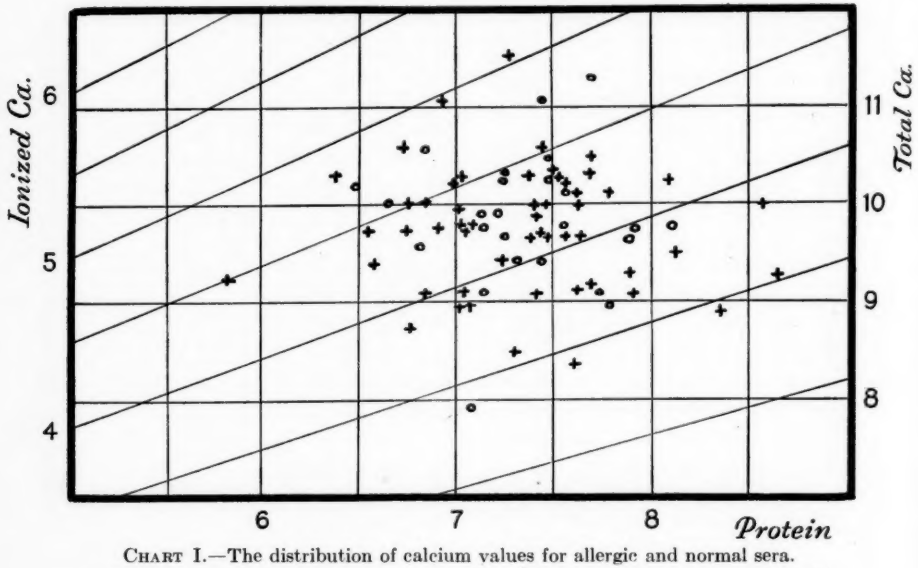

CHART I.—The distribution of calcium values for allergic and normal sera.

Each cross represents an allergic serum, each circle a normal serum. The horizontal lines represent total calcium in mg. per 100 cc., the vertical lines protein in grams per 100 cc. The oblique lines represent the ionized calcium (after McLean and Hastings). If a point is located by determining the total calcium and protein, the ionized calcium is readily estimated from the diagram.

The total calcium was determined by the Tisdall[19] method, using 2 cc. of serum. To check the accuracy of the determination, 3 or 4 analyses were made on each of 6 different sera. The average deviation of a single analysis was ±.35 mg. per 100 cc. In the beginning of the work, a number of determinations were done on 1 cc. samples of serum, but the results were considerably higher and more variable than when a 2 cc. sample was used, so they are not included in the final series.

The total nitrogen was determined by the Kjeldahl method, and the protein nitrogen obtained by subtracting .133, a correction for non-protein nitrogen and blank based on the average of 52 sera studied by Stull, Glidden and Loveless[18] in this laboratory. The error introduced by this step is negligible, since none of the patients included in the series had kidney

disease. The protein determinations could be reproduced with a greater precision than the calcium figures; the average deviation of analyses on a single serum was ±.05 gm. per 100 cc.

Results. Of the 25 normal sera, 21 showed total calciums between 9 and 11 mg. per 100 cc., the usually accepted limits of normal. Two were high and two low, the highest 11.29 and the lowest 7.88. The distribution of the allergic group was essentially the same, 45 of 53 cases falling between 9 and 11 mg., 7 being low (minimum 8.35) and 2 high (maximum 11.52).

When the ionized calcium was calculated, the distribution of cases in the normal and allergic groups was again very similar. Of the 25 normals, 19 were between 3.7 and 4.7, with the highest 4.8 and the lowest 3.3. Among the 53 allergics, 44 fell between 3.7 and 4.7, the highest was 5.0 and the lowest 3.4.

TABLE 1.—CALCIUM VALUES FOR ALLERGIC AND NORMAL SERA.

	Cases.	Total calcium.	Ionized calcium.
Normals	25	9.80 ± .08	4.20 ± .05
All allergies	53	9.74 ± .06	4.20 ± .04
Asthma	31	9.80 ± .09	4.19 ± .04
Hay fever	11	9.52	3.99
Urticaria	5	10.12	4.52
Eczema	4	9.40	4.30
Migraine	2	9.64	4.35

The averages for the two groups are shown in the table. For the total calcium the normal average was 9.80 mg. per 100 cc. with a probable error of ± .08, the average of the allergic group 9.74 ± .06. The difference was well within the limits of error. The average ionized calcium of the normal group was 4.20 ± .05, that of the allergic patients 4.20 ± .04.

The values for the different allergic diseases are also tabulated. The asthmatic group of 31 cases had an average total calcium of 9.80 and an ionized calcium of 4.19. When the asthmatic group was subdivided into purely allergic, infective and mixed cases, the values of each class were nearly the same.

The other four groups, hay fever 11 cases, urticaria 5 cases, eczema 4 cases and allergic (skin-sensitive) migraine 2 cases, all gave figures well within the normal limits and as near the normal average as could be expected with such small numbers of cases. One serum taken during a moderately severe constitutional reaction, following an injection of cottonseed extract, showed a total calcium of 10.35, ionized fraction 4.4.

We feel that if calcium deficiency were a physiologic factor in the occurrence of allergic symptoms, its presence could be demonstrated best by the study of the calcium ion concentration of the serum, since it is the calcium ion that is actually thought to affect permeability and smooth muscle contraction. The method of McLean and Hastings seems especially suitable since it is ultimately based on the

physiologic action on the frog heart, which probably parallels the effects on other tissues. We therefore consider our results evidence against the importance of calcium deficiency as a factor in allergic reactions.

It is of course possible that calcium compounds might show some therapeutic benefit, even though there was no actual deficiency, just as the injection of adrenalin relieves an asthmatic although his body is presumably producing a normal amount of this hormone. We are not prepared to express an opinion on this phase of the problem. We have treated a few cases of persistent asthma with large doses of calcium chloride by mouth and a few with viosterol. Great care was taken to choose cases whose condition was static, and no other change in therapy was made at the same time. One patient improved greatly while receiving calcium chloride, without measurable change in the serum calcium. None of the other cases showed definite benefit.

Summary. The calcium ion concentration in the sera of patients with various allergic diseases showed no significant variation from the normal value. The same was true of the total serum calcium.

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A SURVEY OF UNDULANT FEVER AND BANG'S DISEASE IN THE UNITED STATES.

By Louis Gershenfeld, P.D., B.Sc., Ph.M.,
PROFESSOR OF BACTERIOLOGY AND HYGIENE, PHILADELPHIA COLLEGE OF PHARMACY AND SCIENCE,
AND
Donald C. A. Butts, M.Sc., D.Sc.
PHILADELPHIA, PA.

(From the Department of Bacteriology of the Philadelphia College of Pharmacy and Science.)

In 1887, Bruce[2] isolated the causative agent of undulant fever, which he named Micrococcus melitensis. Other workers revealed that it was, in reality, a rod form and not a coccus, and accordingly

it became known as Bacillus melitensis, and also as Bacterium melitensis. The term Brucella (named after the discoverer), is now usually employed and infections by species of this genus are known today as brucelliasis and brucellosis.

In 1897, Bang,[1] of Copenhagen, isolated a small bacterium, the Bacillus abortus, from the uterine discharges of cows which had aborted. Bovine infectious abortion is frequently designated as Bang's disease. In 1918, the classic work of Miss Alice Evans,[4] brought together the two diseases—Malta fever in man, and infectious abortion in cattle. In 1924, Keefer[5] reported a definite case of human infection with Bacillus (now known as Brucella) abortus. Carpenter,[3] and others, later succeeded in isolating the latter organism from the blood and various lesions of many patients.

The infectious abortion of swine, caused by the porcine strain, Brucella suis, is also pathogenic for both man and cattle. In districts where hog raising is carried on, it is recognized that this animal and the porcine strain, may be the source and cause of human infections.

The results of the numerous investigations during recent years have led workers to the following conclusion: brucellosis in man and animals is a widespread disease in this and other countries throughout the world. Though some workers regard the causative agent of infectious abortion in cattle and that of undulant fever in man as very similar, with serologic distinctions as the only difference, others regard the relationship as still an open question. In man, the bovine caprine (from goats) and porcine types of brucellosis have been found. In this country, the caprine type is relatively infrequent. It is known that in some regions sheep are infected, and it is possible that a distinct ovine strain of brucella exists. Recently horses have also been proven to be sources of infection.

Infected raw milk or its products, direct contact with the flesh or discharges from infected animals (either diseased or carriers), and improperly cooked meat from such animals are, in the light of our present day knowledge, the principal source of the infection in man.

The possibility of untreated water, contaminated with the urine or discharges (or even with raw milk) of affected animals or carriers, and even insect vectors serving as a source of the spread of brucellosis, must be kept in mind.

It is impossible to estimate the extent of brucellosis in man and in cattle, as exact statistical records are not available. Furthermore, it is known that the vast majority of cases that occur in man remain unrecognized. The same disease has been confused with other diseases. In many instances, due to the mildness of the infection, an exact diagnosis is not made; and in other instances, for any of several reasons, known cases of undulant fever may not have been reported to the health authorities.

In preparing for a plan of investigation, to be reported at a later date by one of the authors, a thorough statistical study of the prevalence and mortality of undulant fever was deemed advisable. Such a study,* together with a survey of the distribution and prevalence of Bang's disease, was initiated with the hope that it might bring to light data of significance in a more comprehensive understanding of human brucellosis.

The results of a questionnaire sent to several European countries are given in Table 1.

TABLE 1.—UNDULANT FEVER IN EUROPEAN COUNTRIES (1930–1935).

Country.	Year.					
	1930.	1931.	1932.	1933.	1934.	1935.
England . . .	30	42	65	62	52	39
France . . .	*	*	293	392	424	*
Germany . . .	626†	520†	498†	483†	530†	513†
Italy	1156	1454	1997	1923	2896	2750
Netherlands . .	18	23	21	27	34	25

* No report.

† October 1 (previous year) to September 30 (inclusive).

The information in Table 2 was obtained in response to a questionnaire sent to the Health Department in each state. Our data includes only those cases actually reported to the health authorities. A number of the states included the number of reported cases of undulant fever for the year 1935. Of the 21 states making this report, 13 showed an increase over 1934, the remaining 8 states showed a decrease in 1935. The total number of cases referred to hereafter, includes those in all states in the United States, excepting South Dakota from which state information was not available.

Our survey showed a total of 9317 cases of undulant fever reported in the United States for the years 1928 to 1934 inclusive. Comparison of the incidence in several European countries with that in the United States is shown in Table 3.

The figures shown under "Mortality Rate for Undulant Fever" in Table 4, were obtained from the number of cases, as reported by the individual states, and the number of deaths, as reported by the United States Census Bureau.

Discussion. Analysis revealed many interesting facts, some of which have been reported previously by various workers. The following are also of interest:

One would expect to find some correlation between the number of infected herds revealing Bang's disease, or at least the percentage

* This presentation has been made possible only by the excellent coöperation of the many individuals and organizations who have so kindly assisted us in the accumulation of this data. We are greatly indebted to the United States Bureau of the Census, to the Bureau of Animal Industry and the Bureau of Entomology and Plant Quarantine of the United States Department of Agriculture, and to the Health Departments of the individual states throughout the country for the assistance they have rendered. We are also indebted to the officials in the several foreign countries who have forwarded to us the data included in this report.

TABLE 2.—REPORTED CASES OF UNDULANT FEVER (BY INDIVIDUAL STATES) (1928–1934).

States.	1928.	1929.	1930.	1931.	1932.	1933.	1934.	Total 1928–1934.
Alabama	..	17	23	20	17	12	45	134
Arizona	6	12	21	12	10	27	18	106
Arkansas	*	*	*	2	1	10	10	23
California	11	73	120	106	109	136	158	713
Colorado	1	5	2	7	5	4	7	31
Connecticut	4	12	21	20	33	36	55	181
Delaware	*	1	7	2	2	6	10	28
Florida	..	8	4	3	2	5	9	31
Georgia	10	14	10	8	35	39	63	179
Idaho	*	*	*	*	*	51	3	54
Illinois	1	39	63	124	72	94	101	494
Indiana	..	..	35	27	30	17	18	127
Iowa	118	174	145	48	85	151	187	908
Kansas	14	85	99	64	79	86	99	526
Kentucky	11	13	8	20	7	8	8	75
Louisiana	2	17	20	59	35	28	54	215
Maine	8	8	10	5	16	27	27	101
Maryland	11	18	32	47	49	39	49	245
Massachusetts	*	*	6	15	15	11	15	62
Michigan	8	4	14	19	45	81	101	272
Minnesota	12	42	62	72	62	72	102	424
Mississippi	..	..	..	..	11	13	3	27
Missouri	*	50	135	162	179	79	54	659
Montana	2	3	4	4	11	16	15	55
Nebraska	..	1	..	4	1	..	4	10
Nevada	..	2	..	..	1	..	..	3
New Hampshire	..	..	..	1	4	9	9	23
New Jersey	A	A	14	49	36	28	27	154
New Mexico	1	2	2	5	3	7	5	25
New York	B	106 B	157	171	223	255	301	1213
North Carolina	C	C	C	C	4	15	19	38
North Dakota	5	5	10	42	1	4	5	72
Ohio	11	29	84	118	84	56	66	448
Oklahoma	..	4	2	13	5	15	4	43
Oregon	13 D	19	24	24	22	25	34	161
Pennsylvania	3	25	35	33	47	54	80	277
Rhode Island	..	3	2	..	1	11	9	26
South Carolina	2	17	4	2	5	2	20	52
South Dakota	*	*	*	*	*	*	*	*
Tennessee	2	2	11	7	10	12	4	48
Texas	..	3	5	11	31	43	21	114
Utah	1	3	2	8	7	11	33	65
Vermont	2 E	4 E	19	16	13	14	25	93
Virginia	3	4	25	20	37	46	33	168
Washington	*	22	26	34	18	24	25	149
West Virginia	*	*	1	..	1	2	2	6
Wisconsin	8	42	83	71	59	104	86	453
Wyoming	..	2	2	..	..	2	..	6
Total in the U. S.	270	890	1349	1475	1523	1787	2023	9317

* (Data not available or not given)
.. (No cases reported)
A (Reportable beginning July, 1930)
B (Reportable beginning July, 1929)
C (Reportable beginning 1932)
D (July to December)
E (Actual records commence in 1930)

of positive reactors among the cattle of the infected herds in a state, and the corresponding number of cases of undulant fever in that same state. These statistics do not necessarily reveal this information. Let us, for example, analyze the following two groups of states. One we will designate as the "High Morbidity Rate,"

TABLE 3.—REPORTED UNDULANT FEVER CASES IN EUROPEAN COUNTRIES AND THE UNITED STATES.

Country.	Years.	Total number of reported cases.
England	1926–1935	318
France	1932–1934	1,109
Germany*	1930–1935	3,170
Italy	1924–1935	18,086
Netherlands	1930–1935	148
United States	1928–1934	9,317

* October 1 (previous year) to September 30 (inclusive).

which will consist of those states in which the rate is in excess of 15 cases per 100,000 population; the other group, the "Low Morbidity Rate," will include those states with a rate less than 2 cases per 100,000 population.

	High morbidity rate.			Low morbidity rate.	
State.	No. of cases.	Rate.	State.	No. of cases.	Rate.
1 Wisconsin	453	15.2	Arkansas	23	1.2
2 Minnesota	424	16.5	Mississippi	27	1.3
3 Missouri	659	18.2	Tennessee	48	1.8
4 Kansas	526	28.0	Oklahoma	43	1.8
5 Iowa	908	36.7	Massachusetts	62	1.5
6 Arizona	106	24.3	N. Carolina	38	1.2
7 Oregon	161	16.9	W. Virginia	6	0.3
8 Vermont	93	25.9			

The following reveals the percentage of herds containing infection, and the percentage of reactors among the cattle of the infected herds of the previously mentioned states.

State.	Percentage of infected herds.	Percentage of reactors.	State.	Percentage of infected herds.	Percentage of reactors.
1 Wisconsin	31.1	19.3	Arkansas	15.1	15.2
2 Minnesota	38.0	17.8	Mississippi	60.4	9.0
3 Missouri	31.9	18.1	Tennessee	65.2	12.7
4 Kansas	57.6	19.9	Oklahoma	48.7	13.4
5 Iowa	57.9	22.0	Massachusetts	51.3	15.6
6 Arizona	28.2	10.6	N. Carolina	35.0	11.0
7 Oregon	18.4	14.8	W. Virginia	9.8	16.9
8 Vermont	49.3	15.2			
Average	39.05	17.2		40.8	13.4

From these last two tables we learn that there was a high percentage of infected herds in those states showing a low morbidity rate for undulant fever, though the percentage of reactors was somewhat less, yet not proportional to the existent morbidity rate of undulant fever cases. Attempted correlation of data from other

TABLE 4.—INCIDENCE, MORBIDITY AND MORTALITY OF UNDULANT FEVER, AND DATA CONCERNING BANG'S DISEASE IN THE UNITED STATES.

Registration area.	Undulant fever. Population 1930.	Cases reported 1928–1934.	Cases per 100 000 population.*	Deaths reported 1928–1934.	Mortality rate.*	Bang's disease. Herds tested.	Total No. of cattle tested.	Herds containing infection.	% of herds containing infection.*	Total No. of cattle in infected herds.	Number of reactors.	% of reactors in infected herds.*	% of reactors in total number of cattle tested.*
Alabama	2,645,297	134	5.0	10	7.5	4,333	313,651	2,874	66.3	257,804	23,244	9.0	7.4
Arizona	435,833	106	24.3	3	2.8	1,855	36,058	523	28.2	20,033	2,121	10.6	5.9
Arkansas	1,854,482	23	1.2	5	21.7	29,927	238,922	4,527	15.1	100,227	15,269	15.2	6.4
California	5,672,009	713	12.6	16	2.2	128	8,121	61	47.7	5,119	523	10.2	6.4
Colorado	1,035,043	31	3.0	1	3.2	409	20,889	201	49.1	15,191	1,518	10.0	7.3
Connecticut	1,604,711	181	11.3	2	1.1	611	19,547	332	54.3	11,887	1,631	13.7	8.3
Delaware	238,380	28	11.7	1	3.6	1,381	25,409	508	36.8	11,689	2,031	17.4	8.0
Florida	1,466,625	31	2.1	4	12.9	9,586	236,311	3,430	35.8	162,597	22,606	13.3	9.6
Georgia	2,902,443	179	6.2	7	3.9	3,857	138,290	1,792	46.5	90,757	9,573	10.6	6.9
Idaho	445,837	54	12.0	7	13.0	18,555	201,688	6,010	32.4	93,032	13,498	14.5	6.7
Illinois	7,607,684	494	6.5	18	3.6	14,908	242,856	6,765	45.4	138,088	27,818	20.1	11.5
Indiana	3,225,600	127	3.9	16	12.6	23,714	305,158	9,341	39.4	150,763	28,240	18.7	9.3
Iowa	2,467,900	908	36.7	25	2.8	14,900	271,100	8,636	57.9	189,918	41,763	22.0	15.4
Kansas	1,879,946	526	28.0	20	3.8	6,462	178,298	3,724	57.6	130,632	25,994	19.9	14.6
Kentucky	2,623,668	75	2.8	10	13.3	28,064	300,915	7,184	25.6	127,478	22,774	17.9	7.6
Louisiana	2,094,496	215	10.3	16	7.4	5,062	147,590	1,969	38.9	106,610	13,640	12.8	9.2
Maine	797,423	101	12.6	3	3.0	3,211	48,447	1,138	35.4	23,487	4,209	17.9	8.6
Maryland	1,629,321	245	15.0	4	1.6	8,144	91,919	2,298	28.2	44,745	7,158	16.0	7.8
Massachusetts	4,253,646	62	1.5	0	0	273	8,634	140	51.3	4,974	776	15.6	9.0
Michigan	4,842,280	272	5.6	17	6.3	26,691	318,838	6,209	23.3	103,724	21,433	20.7	6.7
Minnesota	2,566,445	424	16.5	4	0.9	68,042	1,059,814	25,893	38.0	508,099	90,254	17.8	8.5
Mississippi	2,007,979	27	1.3	3	11.1	5,302	135,918	3,203	60.4	112,372	10,130	9.0	7.5
Missouri	3,620,961	659	18.2	20	3.0	47,874	602,420	15,288	31.9	270,970	49,130	18.1	8.2
Montana	536,332	55	10.2	1	1.8	7,699	174,480	2,238	29.1	94,100	14,555	15.5	8.3
Nebraska†	1,378,900	10	7.2	4	40.0	5,736	103,258	2,206	38.5	57,369	9,795	17.1	9.5
Nevada	90,891	3	3.3	1	33.3	1,917	34,520	835	43.5	21,822	2,701	12.4	7.8
New Hampshire	465,293	23	4.9	1	4.3	2,248	33,343	824	36.7	16,481	2,907	17.6	8.7
New Jersey (A)	4 028,027	154	3.8	6	3.9	834	57,818	501	60.1	49,685	2,640	5.3	4.6
New Mexico	427,216	25	5.8	4	16.0	4,100	90,458	842	20.5	44,241	3,802	8.6	4.2
New York (B)	12,619,503	1213	9.6	24	2.0	6,962	174,058	3,702	53.2	118,432	11,361	9.6	6.5
North Carolina (C)	3,170,287	38	1.2	13	34.2	7,309	168,331	2,560	35.0	80,953	8,870	11.0	5.3
North Dakota	682,448	72	10.6	1	1.4	7,737	128,185	1,832	23.7	43,972	9,319	21.2	7.3
Ohio	6,689,837	448	6.7	34	7.5	37,878	432,961	11,786	31.1	170,428	39,120	23.0	9.0
Oklahoma	2,391,777	43	1.8	7	16.3	31,292	719,525	15,226	48.7	496,403	66,538	13.4	9.2
Oregon	952,691	161	16.9	4	2.5	54,239	609,933	9,985	18.4	261,479	38,774	14.8	6.4
Pennsylvania	9,640,802	277	2.9	16	5.8	25,402	379,338	5,580	22.0	135,197	22,903	16.9	6.0
Rhode Island	687,232	26	3.8	1	3.8	64	2,398	39	60.9	1,726	240	13.9	10.0
South Carolina	1,732,567	52	3.0	2	3.8	3,829	93,094	1,085	28.3	44,964	4,705	10.5	5.1
South Dakota (D)	690,755	(D)	....	1	....	578	18,282	312	54.0	12,837	2,335	18.2	12.8
Tennessee	2,608,759	48	1.8	3	6.3	12,331	234,593	8,044	65.2	187,231	23,747	12.7	10.1
Texas	5,821,272	114	2.0	9	7.9	8,925	366,526	4,462	50.0	263,456	38,576	14.6	10.5
Utah	502,582	65	13.0	1	1.5	15,835	114,486	3,096	19.6	47,431	7,482	15.8	6.5
Vermont	359,611	93	25.9	1	1.1	994	32,121	490	49.3	18,739	2,853	15.2	8.9
Virginia	2,419,471	168	6.9	10	5.9	109,991	621,736	9,345	8.5	181,734	23,668	13.0	3.8
Washington	1,561,967.	149	9.5	5	3.4	41,305	381,315	9,191	22.3	169,433	31,316	18.5	8.2
West Virginia	1,728,510	6	0.3	1	16.7	28,473	195,533	2,806	9.8	42,472	7,170	16.9	3.7
Wisconsin	2,980,282	453	15.2	11	2.4	92,354	1,673,167	28,759	31.1	649,148	125,559	19.3	7.5
Wyoming	224,597	6	2.7	1	16.7	1,864	68,607	749	40.2	46,790	5,114	10.9	7.5
Totals and averages	122,309,618	9317	8.7	374	7.9	833,185	11,858,859	238,541	38.4	5,936,719	941,383	14.9	8.0

† (See explanation under text)

(A) Cases not reportable until July 1, 1930, no deaths reported for 1928–1929.

(B) Cases not reportable until July, 1929, 1 death reported in 1928.

(C) Cases not reportable until 1932; 6 deaths reported for 1928 and 1931.

(D) Data on cases not available, 1 death reported in 1933.

* Calculated by authors.

states, let us say Arizona and Mississippi, shows that in the latter state there was a very low morbidity rate for undulant fever, an exceedingly high percentage of herds infected with Bang's disease, and a correspondingly high percentage of reactors of the total number of cattle tested. In Arizona, where the morbidity rate was approximately twenty times as high, the percentage of infected herds was less than one-half, and the percentage of reactors was only slightly in excess to that of Mississippi.

It is of course true that data concerning the use of raw and pasteurized milks in these states, and other factors responsible for undulant fever would permit a more intelligent consideration of the above data. We must also keep in mind the reliability of the number of cases, as actually reported to the health authorities.

The tables were arranged as above, inasmuch as the states, numbered from 1 to 5 inclusive in both groups, are adjoining states. Whether or not this is of any significance, requires further study. It appears that environmental factors, and especially the possibility of there being an arthropod vector of the infection, are to be considered. This, however, requires further detailed studies.

Summary. The authors present a survey of undulant fever and Bang's disease in the United States, with the hope that it may assist others who may be encouraged to further studies along the lines indicated in our discussion.

We cannot urge the respective State Departments of Health too heartily, that they inaugurate campaigns to supply, as well as to obtain, more exacting information concerning undulant fever in this country.

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CONVALESCENCE.

WITH SPECIAL REFERENCE TO THE PHILADELPHIA AREA.

BY J. H. CLOUD, M.D.,
ARDMORE, PA.
MEMBER OF STAFF, THE BRYN MAWR HOSPITAL, BRYN MAWR, PA.

"A CONVALESCENT patient is one who has passed the acute stages of illness or operation—but who is not yet able to resume his normal mode of life." It is most necessary to distinguish between the convalescent, who will regain normal health within a short period, and the patient suffering from chronic disease, who will probably require special treatment for a long period.

Except for the publications of the Sturgis Foundation of New York, relatively few contributions on the subject of convalescence have appeared in the current medical journals. In book form, however, three important publications may be mentioned. In 1927, John Bryant,[2] published a comprehensive volume; in 1930, Dr. Corwin and Mr. Kidner[3] contributed their work through the Sturgis Fund of the Burke Foundation in New York, and in 1935, a book by Elizabeth Green Gardiner,[5] was published.

Although according to Bryant, there is ample evidence that this aspect of medicine was not ignored even in antiquity, and numerous references may be found in the writings of Hippocrates, Celsus and others regarding regulation of diet and exercise for patients recovering from acute disease, yet descriptions of special homes or hospitals for convalescents do not appear until the middle of the 17th century. At that time certain wards in the Hotel Dieu and the Charité Hospital in France were set aside for convalescing patients. In 1781, a French Royal ordinance was decreed establishing accommodation for these cases either in separate hospitals or on the ground floor of general hospitals. However, the extra beds were soon required to care for acutely ill patients, and for many years nothing further was heard concerning them. Napoleon III provided for the organization of convalescent hospitals for the poorer classes in 1855. The Convalescent Hospital of Vincennes, near Paris, was opened in 1867, with eventual accommodation for 552 patients. It is interesting to note that the patients were permitted to engage in various duties, such as repair of clothing and furniture, at a small cash compensation, and that the hospital boasted a library and music room as well as equipment for hydrotherapy and electric treatments. A similar home, known as the Hospital of Vesinet, was opened for women of the working class in 1859. There were several private convalescent homes for the poor and for children, as well as provision for convalescent soldiers; but after the World War, there were no funds for keeping these institutions alive and both Vincennes and Vesinet sank into oblivion, unless revived in the last few years.

The United States seems to have been peculiarly backward in recognizing the importance of this phase of medical care. Even as far back as 1882, a "roving correspondent" reporting in a British journal, *The Lancet*, on his visit to the first convalescent institution ever established in the United States, comments upon the strange fact that "with all the progressive genius for which the Americans are famed, for some unexplained reason they have not heretofore recognized the advantage of the convalescent hospital." This first convalescent institution to be established in the United States, the Waverly Convalescent Home, was founded by Miss Mary Russell, and was directed by the Massachusetts General Hospital. It had 30 beds and two wards of 9 beds each. The correspondent

remarks upon the admirable management, cleanliness and cheer of the home, adding that he had never "seen a more model institution," and that the British might do well to emulate its good points in their more numerous establishments. This comment of 1882 has not changed much in tone even in the most recent report on convalescent institutions in Great Britain by Gardiner, 1935, who likewise emphasizes our great dearth of institutions, but our superior equipment and management.

In 1908, Armstrong[1] drew attention to the fact that 44% of the 31,334 patients discharged from Bellevue were not fit to work, and that 30% were in need of further treatment. In 1915, the Winifred Masterson Burke Relief Foundation, with a legacy of several million dollars, was opened for the purpose of providing free care to the convalescents of New York. It had 300 beds, a receiving office in the city, and special bus transportation. In 1916, Frederic Brush contributed an important paper on "Convalescence in the United States." He felt it unnecessary to review the history of British convalescent homes, because he believed that this country would develop its own type. However, it is interesting to know that as early as 1610, such a house was opened in Bath, Somersetshire, England, to remedy the crowding of the city of Bath with sick poor. In fact, the need for convalescent hospitals in general, is always found to be largely based upon the lack of accommodation for acute cases in the hospitals, necessitating early discharge to make room for new cases, and upon the poor housing conditions of the working class which constitute a real menace to the weak, freshly recovered patient with risk of relapse and chronic invalidization. The better class can easily be accommodated in the more expensive, privately conducted institutions.

With an annual discharge of some 40,000 to 70,000 patients needing convalescent care from the hospitals of New York City alone, it is evident that not even so admirable an institution as the Burke Relief Foundation, accommodating 10,000 patients annually, can cope with this situation. Increasing incidence and of mortality from chronic diseases indicate the crying need for expansion in this field. For this reason, Brush has suggested a plan for central government supervision on a nation wide scale. The New York Medical Center has provided a clearing house, giving daily information as to available beds in convalescent homes. A National Directory of Convalescent Houses has been issued, as well as a directory for convalescent homes serving New York City.

Although the population of the United States is 2.7 times as great as that of Great Britain, and the United States covers an area 33.5 times as large as Great Britain, we have only 179 convalescent homes (1935) as compared with 431 in Great Britain, or 7.1 beds per 100,000 population as compared with 53.6 beds per 100,000 in Great Britain. These figures are taken from Gardiner's book, in

which attention is also called to the fact that in 24 of our states we have no institutions for convalescence whatsoever. Both in Great Britain and Russia the trade unions have contributed their part in establishing convalescent homes for their members. In Russia, where the trade unions play a dominant part in control of the government, Houses of Rest, where adequate convalescent care may be obtained, are maintained not only inside and outside of every city, but also in the various seashore and country summer resorts. Medical treatment, regulated diet and rest, hydrotherapy and means of recreation are provided. The requirements for admission are the same as those demanded in sanitaria. Here in the United States a number of the larger industrial corporations maintain rest homes for their employees. The Philadelphia Electric Company maintains a house in Maryland, where its employees may board for a period of 2 weeks at a very small charge, until they regain their strength. It has accommodations for from 12 to 18 guests.

Needless to say that in this country where until most recently the whole problem has been grossly neglected, provision for special sections of the population, such as the colored people, for instance, has been almost entirely ignored.

According to Bryant, however, the interest aroused in the subject has given impetus to plans on an unprecedented scale, and with our great wealth and greater advances in occupational and dietetic management, there can be no doubt that within a few years our convalescent institutions should lead the world.

Occupational Therapy. Occupational therapy was recognized as a most important adjunct in the treatment of the convalescent sick even in the days of the early Egyptians (2000 B.C.). In 172 A.D. Galen wrote, "Employment is Nature's best physician and is essential to human happiness."

Benjamin Rush emphasized the importance of occupational therapy and recreation in restoration of health. He provided facilities for sewing and embroidery for his women patients, and for farming, carpentry and shoe repairing for his men patients. It was not until 1906, however, that the first school for occupational therapy was opened (Boston) and in 1914, a course in that branch was opened at Teachers' College, New York. In Philadelphia there is the School for Occupational Therapy. There are departments of occupational therapy in nearly all our large hospitals, and this branch of treatment is rapidly becoming recognized as of prime importance in building up and restoring health to convalescent patients.

Government Supervision in England. In England, the types of organizations responsible for the management of its convalescent homes are varied: 82.4% of the institutions in that country are still supported by private philanthropy, including religious groups, social

agencies, charitable trusts and employers, hospitals and voluntary committees. Most of the homes run by the hospitals for their own patients were small, only 7 of 84 containing more than 50 beds.

An effective form of government supervision is made by the Ministry of Health in the form of grants to local authorities and to voluntary committees. According to Gardiner, these grants have been made "to agencies providing care for many different stages of illness, including some convalescent homes. As a method of supervision the giving of grants has been effective because: 1, the plan is carefully worked out by the voluntary committee and the local authority before it is presented to the Ministry; 2, the acceptance of the plan gives the Ministry the right (*a*) to inspect the institution, (*b*) to audit the account, and (*c*) to diminish or discontinue the grant for non-fulfillment of the agreement. This is ample safeguard to the standards of physical care, given if, as in Great Britain, the central authority has a high standard. Through the National Health Insurance Fund central government money goes to the convalescent homes in two ways, namely: (*a*) as per capita payments from approved societies, both mutual and industrial, coming under the heading of additional benefits, but often listed with other fees in annual reports of voluntary agencies; and (*b*) grants of lump sums to reserve accommodations for members, or to encourage homes to continue. It is important to remember in this connection that the British plan is both contributory and compulsory; therefore, two-thirds of the money dispensed under this Act had been previously paid by the worker and the employer to the government. Only approximately one-third of the money expended under the National Health Insurance Acts can be called public money in the sense of taxpayers' money."

A few years ago a Committee of the New York Academy of Medicine took up the question of convalescent care and suggested certain standards that should be maintained. The requirements were published by the Welfare Council of New York City under the title of "Minimum Standards for Convalescent Homes," and were used by several institutions in the neighborhood of Philadelphia.

Basis for Estimation of Required Number of Community Beds. A careful survey of the Philadelphia Hospitals was made in 1929 by Dr. Haven Emerson.[4] In the chapter devoted to convalescent facilities, he states that, "In determining the number of beds which should be provided for institutional convalescent care for patients, who have gone through the critical hazards of acute illness, it is the practice to estimate that such cases will equal 10% of all patients receiving hospital care with 2% additional to provide for patients in need of such services attending out-patient department clinics. On this basis, Philadelphia, with 200,000 patients annually, would have approximately 24,000 patients needing convalescent care each year. At the rate of 17 patients per bed during the year, each

patient having 3 weeks of care, there are required to meet this need, about 1400 beds." Actually, the total number of beds now available is less than 650, a large percentage being in the state of New Jersey.

Ten years ago, under the auspices of the Council of Social Agencies of the Philadelphia Welfare Federation, a special study of facilities for institutional care was made. It was shown that only 27% of 2083 patients needing this care received this service; of the 1523 not served, 1410 did not receive the care because of lack of beds. In a census taken in December, 1928, and January, 1929, in 48 hospitals for patients with acute illness, 426 out of 6030 patients (7%) were classed as convalescent. In other words, in every acute ward, there were a few individuals, who should have been sent from the hospital, and who needed only a quiet, restful regime, such as could be obtained in a convalescent home at one-third to one-half the cost; and a patient's discharge from a hospital leaves available one more bed for an acutely ill patient. According to Dr. Emerson the *per capita per diem* cost of convalescent care has ranged in the past from $1.75 to $2.25, depending on the size of the Home. The cost is increased if the paid personnel is relatively large. One employee to 5 patients is generally found adequate, in Dr. Emerson's view. From the attached table, p. 691, this does not seem to be the case.

Convalescent Care in the Philadelphia Area. Although New York City stands first in the care of its convalescents, there are in and around Philadelphia a number of institutions for this purpose. As a very good example, the Dunwoody Home for Convalescent Men at Newtown Square, Pennsylvania, may be cited. It was established through the generosity of the late William Hood Dunwoody, and opened in 1924 on a farm of 122 acres, a short distance from Philadelphia, with a capacity of 45 beds. The buildings are of fireproof construction, and it is said that if finances will permit, end pavilions will be added, increasing the number to 60 beds. All of the bedrooms have a southern exposure.

While certain duties are required of the guests, much emphasis is placed on opportunity for rest and diversion. There are rooms for shuffle-board, pool, billiards and ping-pong. The craze for miniature golf which swept the country a few years ago suggested the establishment of a course at Dunwoody. This has proved an ideal form of recreation for the guests, being most suitable for cardiac patients. Teams are formed, adding the zest of competition. Milk contributes much to the health of the patients and likewise to their gain in weight; in some institutions it has been considered too expensive. At this Home, where inspected raw Ayrshire milk is given freely in the diet, it was found that the gain in weight was most striking.

Another outstanding institution is the Children's Heart Hospital at Bala—in the country, on the edge of the city. The Philadelphia

TABLE 1.—CONVALESCENT HOMES IN THE PHILADELPHIA AREA.

	Beds	Personnel	Weekly charge	Waiting list	Average stay (weeks)	Cost per capita per day	Occupational therapy	Nurses	Physician	Type of patients*					Remarks
										Women (white)	Men (white)	Children (white)	Children (colored)	Women (colored)	
Convalescent Hospital, Broomall, Pa.	31	9	$5 to $20	At times	3–4	$2.50	++	+	Visiting	Yes	..	Girls over 10 years	..	..	Occupational therapy highly regarded.
Dunwoody Home, Newtown Square, Pa.	45	17	No charge unless able to pay	Yes	3–4	2.37	–	+	Visiting	..	+	Boys over 18 years			Occupat. ther. may be started this fall.
Ivy Croft Farm, Wayne, Pa.	16	5	Nothing up to $10	No except in summer	3	2.67	++	+	Visiting	..	+	..	..	..	Occupational therapy helps to pay for itself.
Willow Crest Convalescent Home, Willow Grove, Pa.	80	30	About 50% free $7–21	Yes	3	1.86	+	+	Visiting	+	+	+			
James C. Smith Memorial Home, Oakbourne. Pa.	22	5	Free	In summer	2	1.80	+	+	Visiting	+ over 21 years	..	..	..	..	Cost of maintaining home for 1936, $11,419.63. Number of patient days 6345: average $1.80.
Cinnaminson Home, Riverton, N. J.	27 cribs 3	4	Admission $2 mother and baby $3	At times	2	Not given; cost per meal 7c.	+	+	Visiting	+	..	Babies			
Mercer Memorial Home, Atlantic City, N. J.	Summer 134	33	$5 to $7	Yes	2–5	1.67	–	+	Visiting	+					
	All yr. 50														
St. Francis Country Home, Darby, Pa.	27	5	Free	No	2 or more	Less than $2	–	+	Visiting staff	+	..	..	..	..	No waiting, last 2 years. Many inquiries for care of chronic cases.
Children's Heart Hospital, Bala, Pa.	50	16	$3 Med. care	Yes	9 mos.	1.95	Given schooling	+	Visiting staff	..	..	+	+	..	One attendant to 10 children.
Children's Seashore House, Atlantic City, N. J.	All year 145	56 In summer 30 extra	$5 (if able to pay)	..	Several months	1.19 to 1.37	Given schooling	+	Physician in charge	+ mothers	..	+	+	..	Reduction in number of cases of bone and joint tuberculosis. Increase of cardiac cases.
Convalescent Hospital for Colored Women, 1504 Catharine Street, Philadelphia	25	6	$7 ($20 private room)	Often	4	1.75 to 2.05	+	+	Visiting	..	..	..	..	+	
Richard Home, Devon, Pa.	72	Not in operation													

* There are no convalescent beds for colored men.

Heart Association sponsors it for the care of cardiac children. While there are 75 beds, at present only 50 children are being cared for, owing to lack of finances. The children admitted are under close observation and rest for a prolonged time.

A modern convalescent Home is Willow Crest, under the auspices of the Federation of Jewish Charities. Here an experiment is being conducted in the long term care of children with mild forms of rheumatic infection, with the view of preventing development of serious cardiac disease in later life.

FIG. 1.—"The Dunwoody Home," Newtown Square, Pa.

At Atlantic City, New Jersey, may be mentioned the Mercer Memorial House for Woman, as Philadelphia is the source of the majority of its patients.

There is a great opportunity awaiting the Magee Memorial Hospital for Convalescents. Anna J. Magee in her will (1917) endowed this institution, the object of which is to relieve the general hospitals of Philadelphia from the burden of support of patients who have passed through the active stages of acute illness. The Hospital is to be governed by a Board of 12 trustees, each hospital having the right to elect a member. Children under 14 are excluded. The trustees have decided to accumulate this fund until they have sufficient money to put up buildings, leaving a sufficient fund for endowment.

The Supplee Fund is another welcome aid to convalescent homes in the Philadelphia area. This insurance fund of $200,000 is administered by the Board of City Trusts. Any patient in a Philadelphia hospital (except the Philadelphia General) who needs further care is eligible. The board bill at an existing convalescent home is paid by the Board of City Trusts, the maximum allowance being $20 per week, and the maximum time of care 4 weeks.

The facilities for convalescent care would be increased if physicians could become *convalescent-conscious*—if the phrase may be coined.

Pa.

* There are no convalescent beds for colored men.

Inquiry brings out the fact that there has been almost no advance in the number of available convalescent beds in the past 7 years; in fact, two Homes have fewer beds. One, listed in 1929 as having 35 beds, has only 27 beds today, and another dropped from 35 to 30 beds.

The Babies' Hospital of Philadelphia used to maintain a country branch at Llanerch, which was open in the summer; but unfortunately has been unable to support it for the past 2 years. The authorities hope that they may have funds available to re-open the Home this coming summer.

In spite of the large colored population, there is absolutely no provision for the care of colored men; and the only convalescent hospital for colored women in Philadelphia is one of 25 beds, with a waiting list at all times. This hospital is receiving some State aid.

Inquiry at the various homes reveals the fact that several have a waiting list. In one year, recently, the number of applicants at Willow Crest was 3000, while with its 80 beds only 886 patients could be cared for annually. It is feared that this comment will be further confirmed when the results of the contemplated survey by the Committee of the Council of Social Agencies of Philadelphia are published.

Central Bureau. A great step in advance would be the establishment of a central bureau in the city for the distribution of patients needing convalescent care. According to the Executive Secretary of the Public Health Committee of the New York Academy of Medicine, Dr. Lewinski-Corwin, "Such a bureau would greatly facilitate the work of placing patients and would obviate the need of making inquiries at each individual institution. Such a clearing house would in time become an important factor in the situation by the accumulation of facts concerning available facilities and the character of the work performed at the different institutions. It would serve also in securing better utilization of the Convalescent Homes than is the case at the present time."

Summary. The present paper is a plea for an increase in the facilities for convalescent care. Much would be gained if the situation were realized by administrative and professional staffs and boards of trustees of hospitals, and the ends desired could be accomplished through meetings and conferences arranged by a committee of the Hospital Association. It is certainly hoped that the interest of public spirited philanthropists may be aroused by medical organizations, hospital staffs and physicians in general.

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CAUSATIVE FACTORS IN THE PRODUCTION OF LAENNEC'S CIRRHOSIS WITH SPECIAL REFERENCE TO SYPHILIS.

By George A. Schumacher, M.D.,
RESIDENT PHYSICIAN, HOSPITAL OF THE UNIVERSITY OF PENNSYLVANIA, PHILADELPHIA.

(From the Department of Pathology of Cornell University Medical College and of the New York Hospital.)

Syphilitic cirrhosis is characterized by conspicuous, fibrous scars often associated with gummata and usually accompanied by considerable deformity of the organ (hepar lobatum). Diffuse nodular cirrhosis (Laennec's cirrhosis) with none of the usual characters of syphilitic cirrhosis has been repeatedly found in association with syphilitic infection.

The clinical association of cirrhosis of the liver with syphilis was noted in a paper by Pearce[9] on the Wassermann reaction published shortly after this test was discovered. He collected from the reports of several investigators a large series of cases in which the Wassermann test had been performed. In this series, cirrhosis, of which the type was usually not specified, occurred 30 times, and in 22 of these cases the Wassermann reaction was positive. Hawkins,[3] on the contrary, stated that atrophic cirrhosis had no direct etiologic relationship to syphilis.

In 1917, Symmers[11] found among the cases of clinically diagnosed atrophic nodular cirrhosis in the wards at Bellevue Hospital 80% with positive Wassermann reactions. Of the cases confirmed at autopsy, 28% were in syphilitic subjects. Wooley[15] reported 3 cases of "hypertrophic" cirrhosis, in 2 of which there was definite evidence of and in 1 the probability of syphilis. In all 3 there was a probability of alcoholism.

In 1200 autopsies studied by Owen[8] there were 19 cases of nodular cirrhosis of the liver and 3 cases of characteristic syphilitic cirrhosis. In 12 of the 19 cases with nodular cirrhosis the Wassermann test had been done, and it was positive in 5 instances. When the cases with no Wassermann tests were included, the incidence of positive syphilis (5 cases with positive Wassermanns and 2 clinically proven cases) was still 37%. There was a history of alcoholism in 6 of the 19 cases of nodular cirrhosis. Both alcoholism and syphilis were present in 4 cases.

Rolleston and McNee[10] believe that congenital syphilis in children may make the liver susceptible to diffuse cirrhosis. They state that occasionally the liver of a child with stigmata of congenital syphilis shows "ordinary" (portal) cirrhosis, distinguishable from the intercellular fibrosis of infants suffering from congenital syphilis. The liver remains vulnerable to subsequent injury so that conditions tending to produce diffuse nodular cirrhosis will more readily produce this change. In other words, congenital syphilis so prepares the soil that cirrhosis may supervene.

In reviewing 2285 autopsies, LeDuc[5] found 101 cases of cirrhosis which he classified as follows: (1) Atrophic cirrhosis (58 cases or 2.5%); (2) "early cirrhosis which generally had the characters suggestive of early atrophic or early syphilitic cirrhosis" (16 cases); (3) syphilitic cirrhosis (19 cases); (4) "Glissonian cirrhosis" (8 cases). Histologic lesions of syphilis in other organs of the body were found in 60.3% of the cases of atrophic cirrhosis (34 out of 58), and in 66.6% of the cases of atrophic cirrhosis and "early cirrhosis" combined (49 out of 74). When all four varieties of cirrhosis were added together, the incidence of histologic evidence of syphilis was found to be 71.2% (72 cases out of 101). LeDuc suggests that the infrequency of atrophic cirrhosis or Laennec's cirrhosis and syphilis found by other observers may be partly explained by the relative infrequency with which they diagnose visceral syphilis.

Present Study. This is based on clinical and autopsy records of the New York Hospital. In 1977 consecutive cases that came to autopsy, cirrhosis of the liver (all types) was found in 74 instances. The type of cirrhosis was determined by the gross characters of the lesion and by examination of microscopic sections. The results of this analysis are seen in the following table:

TABLE 1.—CLASSIFICATION OF TYPES OF CIRRHOSIS AT NEW YORK HOSPITAL.

		Number.	Per cent.
All cases of cirrhosis		74	
1. Diffuse cirrhosis		45	60.8
A. Nodular (Laennec)	44		
B. Smooth hypertrophic (Hanot)	1		
2. Syphilitic (hepar lobatum)		2	2.7
3. Obstructive		8	10.8
4. Cirrhosis with primary tumor of the liver		7	9.5
5. Central cirrhosis with cardiac disease		2	2.7
6. Miscellaneous		10	13.5
A. Hemachromatosis	3		
B. Cirrhosis with toxic necrosis	2		
C. Splenic anemia	3		
D. Non-lipoid histiocytosis	1		
E. Fibrosis with tuberculosis	1		

Of the 74 cases of cirrhosis, 45 (60.8%) were found to be diffuse, 44 falling into the category of nodular or Laennec's cirrhosis (known also as atrophic or portal), and 1 of smooth hypertrophic cirrhosis, fitting the type described by Hanot. Chief interest centered upon these, but the incidence of syphilis and of alcoholism in the entire group was determined.

There were 2 cases of hepar lobatum or syphilitic cirrhosis with definite clinical evidence of syphilis. In one there was no excessive use of alcohol, and in the other the habits in relation to alcohol were unknown. In the latter the histologic examination of the liver showed, in addition to the deep, puckered, cicatricial lesions, a diffusely distributed cirrhosis.

In almost all of the cases of diffuse cirrhosis in which syphilis

was discovered, this disease was incidental and some other condition for which the patient entered the hospital was apparently more significant. In some instances, there was sufficient evidence at hand to prove conclusively the diagnosis of syphilis (history of chancre, 4+ Wassermann, history of treatment, etc.). There were, however, a number of cases in which, from analysis of the records, syphilis could only be classified as "probable," "possible," or "doubtful." Furthermore, there were a few cases which were classified as "unknown" because the patient had entered the hospital moribund, and the past history and serologic tests were omitted. In the figures showing the incidence of syphilis, cases regarded as "possible" or "doubtful" were not included, though the actual presence of syphilis in some of these is not unlikely.

The single case of Hanot's cirrhosis included in the series was definitely associated with syphilis. This individual also used alcohol to marked excess (Autopsy 6402).

Evidence of syphilis obtained from the data found in the history, physical examination, laboratory tests, and postmortem examination of each case is given below:*

Clinical Abstracts. 1. Autopsy 6352. Male, white, aged 39. History of chancre 20 years before admission and of treatment (amount and duration not known). His wife had a miscarriage at 3 months and no other pregnancy. Blood and spinal fluid Wassermann were negative. Examination of the spinal fluid showed 15 lymphocytes per cm.

2. Autopsy 6402. Male, white, aged 50. Blood Wassermann was 2+ with both alcohol and cholesterol antigens. Ascitic fluid Wassermann was 3+ with alcoholic antigen and 4+ with cholesterol antigen.

3. Autopsy 6425. Male, white, aged 74. Patient had a definite history of syphilis 25 years before death and was treated for 2 years.

4. Autopsy 6911. Male, colored, aged 57, had a sore on the penis "some years ago." Blood Wassermann was 4+ with both antigens. Patient had Argyll-Robertson pupils. Spinal fluid showed 30 cells per cm. of which 80% were lymphocytes. Syphilitic aortitis and aortic valvular disease were found at autopsy.

5. Autopsy 6949. Male, white, aged 36, contracted syphilis 12 years prior to admission and received 5 injections of arsphenamine. Blood Wassermann was 4+ with the cholesterol antigen, negative with the alcoholic antigen. Syphilitic aortitis was found at autopsy.

6. Autopsy 7265. Male, white, aged 49. Luetic infection occurred 10 years prior to admission, and there was "some treatment" at that time. The blood Wassermann was negative. The Kline test was 1+.

7. Autopsy 7229. Male, white, aged 47. Blood and spinal fluid Wassermanns were 4+ with both antigens. Syphilitic aortitis was found at autopsy.

8. Autopsy 7301. Male, white, aged 48. Initial lesion was contracted 12 years before death. Three years later the Wassermann was 4+. This became negative 6 years before death. Patient was treated for 4 years. At his last admission the blood Wassermann was anticomplementary and the Kline test was 1+.

9. Autopsy 7522. Male, white, aged 57, had a chancre in his youth. Blood Wassermann was 4+ with both antigens. Autopsy revealed syphilitic aortitis and an aortic aneurysm.

* Cases 1 to 11 were classified as definite syphilis, Cases 12 and 13 as probable, but inconclusive. Possible and doubtful cases of syphilis were not included.

10. Autopsy 7534. Male, white, aged 56, whose wife had 6 miscarriages, and two children died shortly after birth. Blood Wassermann was 4+ with both antigens.

11. Autopsy 8091. Male, white, aged 53, whose wife had 4 miscarriages (possibly induced). The blood Wassermann was 4+.

12. Autopsy 6250. Male, white, aged 56, whose wife had a possible miscarriage. Patient had failing vision for 3 years prior to admission. Blood Wassermann was 2+ with both antigens. Pupils reacted poorly to light and were small.

13. Autopsy 6275. Male, white, aged 57. Blood Wassermann was 4+ with the cholesterol antigen, but negative with the alcoholic antigen.

All of the 13 cases of diffuse cirrhosis with syphilis were in adults. A case of probable syphilis in a boy of 15 is not included in the list of cases of syphilis with diffuse cirrhosis. This child had advanced diffuse cirrhosis of the type of Laennec. The diagnosis of syphilis did not appear on the hospital chart, and the Wassermann reaction was negative, but irregular teeth, scars over the shins, absent pupillary reflexes, and syphilis in the father indicate that the child had suffered from congenital syphilis. The case recalls the contention of Rolleston and McNee that congenital syphilis increases susceptibility to the ordinary form of nodular cirrhosis.

In the 11 cases of cirrhosis classified as miscellaneous (Table 1), 1 case of hemachromatosis had both syphilis and a history of excessive use of alcohol. The liver in this case showed advanced diffuse cirrhosis.

The incidence of syphilis in the various types of cirrhosis is shown in the following table:

TABLE 2.—INCIDENCE OF SYPHILIS IN CASES OF CIRRHOSIS.

Type of cirrhosis.	No	Syphilis					None.
		Definite.	Probable.	Possible.	Doubtful.	Unknown.	
Diffuse . .	45	11	2	2	2	1	27
Syphilitic .	2	2					
Obstructive .	8			1			7
With tumor .	7	1		1		1	4
Central . .	2				1		1
Miscellaneous	10	1			1		8
Total .	74	15	2	4	4	2	47

Increase of the interstitial tissue of the liver was experimentally produced by repeated administration of small quantities of phosphorus by Afrecht (1879), Ackermann (1880), Kronig (1887), and Dinkler (1887)[7]. Whipple and Sperry[14] produced hyaline necrosis in the central portions of the liver lobules by repeated chloroforming of animals. Mertens (1896), according to Opie, produced cirrhosis in rabbits by daily subcutaneous injections of small quantities of chloroform dissolved in liquid paraffin. Cirrhosis of the liver was produced experimentally also by injecting certain types of bacteria into the circulation of animals (Hektoen,[4] Ogata,[6] and others).

Experiments of Opie[7] showed that bacterial infection could influ-

ence and even determine the development of cirrhosis in the liver when the latter was subjected to the injurious effects of a toxic agent such as chloroform. He showed that combined infection with the colon bacillus and intoxication by chloroform produced advanced diffuse cirrhosis. The experimental production of cirrhosis had been inconstant when the infectious or toxic agent was used alone.

Villaret, Benard, and Blum[13] stated that the combination of syphilis and alcohol was responsible for the majority of cases of cirrhosis of the Laennec and Hanot type. They regarded this view as therapeutically important and cited clinical cures in which syphilis had been eliminated before irreparable lesions had become established. In a discussion of the etiologic factors involved in the production of "venous" cirrhosis of the liver, the same authors[12] draw the following conclusions: (1) Alcoholism produces changes in the liver which lower its resistance and allow the localization of a chronic infection; (2) syphilis cannot itself produce "venous" cirrhosis; (3) syphilis produces changes in the portal areas making them more susceptible to the action of alcohol.

Cade[1] concluded that syphilitic infection was frequently associated with alcohol in the genesis of hepatic cirrhosis. He regarded alcohol as an important factor, but one often associated with chronic infection in the production of cirrhosis.

Grenet, Levent, and Pellisier[2] stated that they had never seen a proven case of Laennec's cirrhosis due to syphilis without alcoholism. They believed it probable that excessive use of alcohol (which could produce cirrhosis by itself) lowered the resistance to syphilis, and that syphilis increased the progress of fibrosis.

The long established association of alcoholism with Laennec's cirrhosis and the work of Opie on the production of cirrhosis by combined infection and intoxication suggested the desirability of determining the frequency of alcoholism, occurring alone or in combination with syphilis, in the cases studied. In the 45 cases of diffuse cirrhosis there were 12 in which the history contained no mention of the alcoholic habits of the patient. These were classified as "unknown." In the rest, consumption of alcohol was classified arbitrarily as "excessive," "moderate," and "none." Only those with a history of excessive use of alcohol were regarded as significant though the others were tabulated (Table 3).

TABLE 3.—INCIDENCE OF ALCOHOL IN CASES OF CIRRHOSIS.

Type of cirrhosis.	No.	Consumption of alcohol.				Combined alcoholism and syphilis.
		Excessive.	Moderate.	None.	Unknown.	
Diffuse	45	16	8	9	12	5
Syphilitic	2			1	1	
Obstructive	8	1	2	2	3	
With tumor	7	1	1	3	2	
Central	2				2	
Miscellaneous	10	1		6	3	1
Total	74	19	11	21	23	6

Syphilis was thus (Table 2) associated with diffuse cirrhosis of the liver in 13 out of 45 cases (28.8%). Alcoholic excess was present in 16 (35.5%) of the cases. The two factors were coëxistent in 5 (11.1%) of the cases. If the cases in which alcoholic habits were unknown were excluded, the proportion of cases in which alcoholic excess occurred alone was 48.5%, and the proportion in which both factors were present, 15.1%.

The sex distribution of all the cases of diffuse cirrhosis was compared with that of the cases of diffuse cirrhosis associated with syphilis. In the entire group of cases of diffuse cirrhosis there was a preponderance of males (78%) over females (22%). This preponderance was even more striking in the group with syphilis, all cases of cirrhosis with syphilis being in males.

The average age of all cases of diffuse cirrhosis (51.2 years) was approximately the same as that of the group with syphilis (53 years). In both groups approximately two-thirds of the cases were in the fifth or sixth decade of life.

An effort was made to determine whether there was any correlation between cirrhosis and the duration of the luetic infection. In 7 of 13 cases the approximate duration of infection was known, and had been from 10 to 25 years in 6; in a seventh case the duration of the disease was said to have been "some years." Information regarding treatment was at hand in only 6 cases and, of these, 5 had had treatment of varied duration and 1 had none.

It is noteworthy that in 45 cases of diffuse cirrhosis there was one instance of Graves' disease and one of nodular toxic goiter.

To compare the incidence of syphilis unaccompanied by cirrhosis with that in individuals with cirrhosis, 45 autopsies on patients of the same age and sex as the 45 with diffuse cirrhosis were chosen otherwise at random from the postmortem files. The presence of syphilis in these was determined in the same manner as before, namely by study of the history, clinical findings, laboratory findings, and autopsy protocols. The history with regard to the use of alcohol was noted in each case. Of 45 cases there were only 2 (4.4%) with syphilis, and both of these, with 4+ Wassermanns during life, had syphilitic aortitis at autopsy. Only half of the histories mentioned the presence or absence of excessive intake of alcohol, of which two definite instances were found. The following table summarizes the data obtained from the control group:

TABLE 4.—INCIDENCE OF SYPHILIS, ALCOHOLISM, AND COMBINED FACTORS IN A CONTROL GROUP OF 45 CASES WITHOUT CIRRHOSIS.

	No.	Per cent.
Syphilis	2	4.4
Alcohol in excess	2	4.4
Alcohol in moderation	8	
No alcohol	13	
Alcoholic habits unknown	22	
Syphilis and alcoholic excess	0	0.0

Postmortem records of all the definitely proven cases of syphilis which came to autopsy in the new New York Hospital during 4 years were reviewed to determine the incidence of cirrhosis. Study of the records and microscopic sections revealed among them 3 cases of diffuse cirrhosis, 1 classified as scant or beginning cirrhosis, the other 2 as moderately advanced. Of the latter, 1 had a history of excessive use of alcohol. There were in addition 5 cases of cirrhosis of other types. These data are shown in Table 5.

TABLE 5.—INCIDENCE OF CIRRHOSIS IN 24 CASES OF CLINICALLY PROVEN SYPHILIS THAT CAME TO AUTOPSY.

Cases of syphilis		24
Diffuse cirrhosis		3
Other types:		
Obstructive cirrhosis	2	
Cirrhosis with carcinoma	2	5
Syphilitic (hepar lobatum)	1	
No cirrhosis		16

The foregoing tables show that syphilis and alcoholism and the two combined are much more frequent in association with diffuse cirrhosis of the liver than in persons of the same age and sex with no cirrhosis of the liver. Of 45 persons with diffuse cirrhosis of the liver, at least one-fourth and probably more have had syphilis. Of a small group of persons with syphilis several (3 of 24) had developed cirrhosis.

Summary. 1. Of 45 cases of diffuse cirrhosis including 44 cases of nodular or Laennec's cirrhosis and 1 case of smooth hypertrophic cirrhosis of the type of Hanot, 28.8% had presumptive evidence of syphilis; approximately one-third were known to have used alcohol in excess, or approximately one-half if those cases were excluded whose alcohol habits were unknown; and 11.1% were both luetic and alcoholic (15.1% when the unknowns were excluded).

2. Approximately three-quarters of the cases of diffuse cirrhosis and all of those with diffuse cirrhosis and syphilis were in men. Among the cases in which the duration of infection was known, that is, in less than half of them, there was no instance in which syphilis had been present for less than 10 years.

3. A control group of 45 autopsies with no cirrhosis in persons of the same age and sex as those with diffuse cirrhosis showed that 2 (4.4%) had had syphilis, and 2 had used alcohol in excess. The two factors were combined in no instance.

4. In a group of 24 autopsies on persons with syphilis, diffuse cirrhosis of the liver was found in 3 cases (12.5%).

5. Syphilis long continued in association with alcoholism, and perhaps alone, may cause diffuse cirrhosis of the liver.

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LEIOMYOMA OF THE SMALL INTESTINE.

WITH REPORT OF A CASE WITH FATAL HEMORRHAGE.

BY OPIE NORRIS SMITH, M.D.,

RESIDENT PATHOLOGIST AND ASSISTANT INSTRUCTOR IN PATHOLOGY, UNIVERSITY OF PENNSYLVANIA, PHILADELPHIA, PA.

(From the Gastro-intestinal Section of the Medical Clinic, University Hospital, and the Department of Pathology, School of Medicine, University of Pennsylvania.)

INTESTINAL obstruction through intussusception is generally emphasized as the commonest surgical complication of small intestinal tumors. In primary leiomyomas, however, a review of the literature indicates that grave hemorrhage is equally frequent, and likewise is amenable to surgical intervention if the patient is fortunate enough to be subjected to laparotomy. In such myomas, focal areas of hemorrhagic necrosis are common, and with their confluence the liquefied center may discharge into the lumen of the intestine, this being followed by copious hemorrhage. Exsanguination with syncope and even death is not uncommon under these circumstances. If the bleeding does subside, it almost invariably recurs. Only through surgery can this group of patients be saved. Too frequently, as in the case to be reported, the exact diagnosis is discovered at the autopsy table following fatal exsanguination.

Case Report. A 58-year-old white farmer, previously in good health, vomited copiously at noon on the day following a 300-mile motor trip, and that evening, after severe upper abdominal pain had appeared, profuse emesis recurred. Blood was not visible in the vomitus, and a large fluid stool was not inspected. Upon admission 2 days later to hospital, October 24, 1935 (service of Dr. T. Grier Miller), he was very restless despite sedation, his hemoglobin being 49% and his red cell count 2,900,000. The stools consisted of dark semifluid blood. No mass could be palpated through a well-relaxed abdominal wall. A surgical consultant concurred in the tentative diagnosis of duodenal or jejunal ulcer, and a medical regimen was outlined. He received large transfusions of blood daily, but succumbed from the persistent hemorrhage on the 7th day of his illness.

Autopsy (No. 35–1306, Dr. H. M. Dixon, 1 hr. after death) disclosed less senescent change than was to be expected, but marked ischemia of all organs. The lower half of the ileum and the colon were filled with approximately 2 liters of reddish-black semifluid blood. On the antimesenteric border of the ileum, 220 cm. above the ileocecal valve, its coarsely nodular surface

covered with intact peritoneum, was a 4 cm. spheroidal tumor that had undergone massive central liquefaction and evacuation through a narrow channel into the intestinal lumen. The cavity was pear-shaped, filled with partially clotted blood, and on first inspection was thought to be a Meckel's diverticulum with an annular neoplasm encircling its orifice. Its wall was lined by a smooth layer of necrotic débris, exhibiting the patent lumen of an eroded arteriole. The intestinal tract above this point was grossly normal and virtually empty. No metastases were found.

Microscopic Examination. The tumor showed whorls of smooth muscle cells interspersed with scant connective tissue (confirmed with Van Gieson's stain). The muscle cells exhibited the following cytological characteristics commonly considered as evidence of malignancy from the histopathologic standpoint: short cells with ovoid nuclei, marked variation in size and shape of the tumor cells, variable staining affinity of the nuclei, "giant cells" with multiple nuclei, and extremely thin-walled blood-vessels. No typical mitotic figures were demonstrable. Both layers of the intestinal muscle were interrupted by the tumor, leaving little evidence as to which one was primarily the seat of the neoplasm. The lining of the cavity wall consisted of necrotic débris and inflammatory exudate harboring bacterial colonies, but entirely devoid of mucous membrane. The distal wall of the cavity also consisted of tumor tissue rather than the components of a Meckel's diverticulum, while the peritoneal serosa was intact and free of exudate or adhesions. The tissue has been examined and the diagnosis of "malignant leiomyoma" substantiated by Dr. Joseph McFarland and Dr. Krumbhaar.

The *incidence* of leiomyoma in the alimentary tract is reflected in Table 1. Raiford[6] found 3 myomas among the 82 primary tumors of the small intestine in the Johns Hopkins Hospital records, while Rankin and Newell[7] reported 11 myomas among 35 benign small intestinal tumors from the Mayo Clinic. This leaves little doubt that myomas of the small intestine are far more frequent than the number of reported cases (109) would suggest.

TABLE 1.—CASES OF LEIOMYOMA OF THE ALIMENTARY TRACT.

Site.	Recent reviews in the literature.	Among 36,000 autopsies at Philadelphia General and University Hospitals (not previously reported).
Esophagus	50[8] (all at autopsy)	2
Stomach	321[3]	18
Small intestine	109 (this report)	8
Large intestine	33*[10]	5

* With 51 cases in small intestine.

In a *classification* by Steiner[11] of small intestinal leiomyomas according to their relation to the lumen of the intestine, those projecting into the lumen and predominantly submucosal were called "inner" myomas, while those extending into the peritoneal cavity were described as "outer." No asymptomatic inner myomas have been reported; when located in the duodenum, partial obstruction or ulcer-like pain is common; when situated below the ligament of Treitz, intussusception is the usual result. They remain small and rarely exceed 4 cm. in diameter. The outer myomas grow much larger, often being compared in size to an infant's head, and undergo

focal hemorrhagic necrosis; these areas tend to merge and rupture by permeation through the tumor tissue into the intestinal lumen. The pear-shaped conformation of the resultant cavity closely resembles the pregnant uterus, and the mechanism of the subsequent hemorrhage is somewhat comparable to that of postpartum inertia uteri. Such a shell of tumor tissue grossly mimics a diverticulum, and despite the absence of mucosal lining, at least one specimen[12] strikingly similar to the one here reported has been recorded as a primary leiomyoma of a Meckel's diverticulum.

The *rate of growth* in these tumors appears to be remarkably slow, often stationary. In a number of patients, symptoms persisting for several decades have been alleviated by extirpation of a myoma measuring but a few millimeters in diameter.

The *degree of malignancy* of a leiomyoma cannot be accurately determined upon histologic criteria. Doring[2] and McFarland[5] have pointed out that the only positive proof of malignancy in this tumor is the presence of metastases. As in our own case, many authors have classified their specimens as malignant upon cytologic grounds, but from the clinicians' standpoint, it is noteworthy that only 9 of the 109 tumors reviewed did metastasize. Recurrences have made their appearance years after removal of the original lesion.

Previous reports present meager clinical data for proper analysis. Most of the specimens were reported purely because of their pathologic interest; some were not adequately confirmed histologically; some were presented soon after surgical extirpation without pertinent clinical details; and finally, the nomenclature of this tumor has often changed during the 80 years since the first acceptable report.

I have rejected the reports of certain specimens which consisted preponderantly of fibrous tissue with admixture of muscle cells. I have taken certain license in assuming the location or outcome in some instances when the report implied but did not specifically state such details. The following remarks are intended to supplement the data presented in Chart I.

Inner leiomyomas have not been reported as incidental autopsy discoveries in the absence of antecedent symptoms, but the assumption that few remain asymptomatic is probably fallacious. Whether sessile or pedunculated, they are most frequently likened in size to various nuts or eggs. They are three times as common in the jejunum and ileum as in the duodenum, which accounts for the preponderance of intussusception. No metastases or recurrences have been reported in this group, and only 3 deaths have been cited in the past 25 years.

Ordinary gastro-intestinal Roentgen study may display a defect due to a duodenal myoma, but below the ligament of Treitz it has not been useful in the diagnosis of these tumors. At this hospital, Abbott[1] has conclusively demonstrated a tumor of the jejunum by intestinal intubation, introducing the barium mixture proximal to an

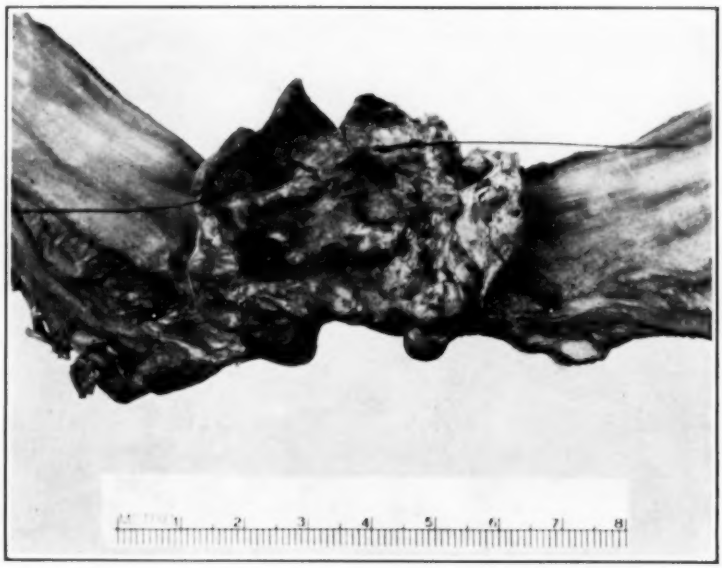

FIG. 1.—Photograph of the opened tumor and serosal surface of the intestine; note the coarsely nodular wall, and the hair inserted in the eroded arteriole. Most of the tumor tissue forms an annular mass around the orifice of the pseudodiverticulum.

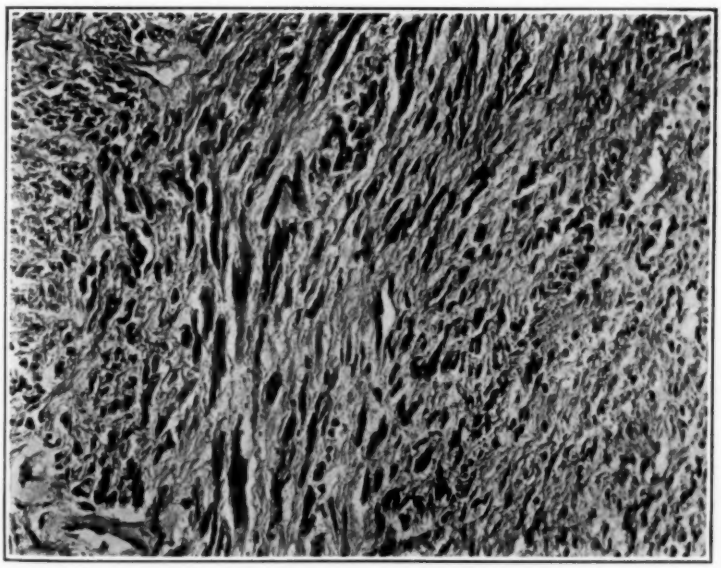

FIG. 2.—Photomicrograph of tumor tissue (hematoxylin-eosin, × 280)

inflated balloon situated beyond the lesion. Such a technique would be well worth attempting in other suspected (but not bleeding) cases of intestinal myoma.

39
"INNER"
SUBMUCOSAL
PEDUNCULATED OR SESSILE
LESS THAN 5 CMS. DIAMETER
70
"OUTER"
SUBSEROSAL
USUALLY ANTIMESENTERIC
7-30 CMS. DIAMETER
27
INTESTINAL OBSTRUCTION
ACUTE CHRONIC
7
SPONTANEOUS HEMORRHAGE
4
CHR. ULCER SYMPTOMS
1
ICTERUS
22
SPONTANEOUS HEMORRHAGE
15
INCIDENTAL AT LAPAROTOMY (13) OR AUTOPSY (12)
13
ABDOMINAL MASS
12
INTESTINAL OBSTRUCTION
ACUTE CHRONIC
5
"INDIGESTION"
3
PERITONITIS (RUPTURE?)
SITE
DUODENUM 0 2 3 2 1 1 4 3 1 1 1
JEJUNUM 3 2 2 0 0 13 2 6 0 1 2 1
ILEUM 14 5 0 0 0 7 6 0 5 2 2 1
"SM. INTESTINE" 1 0 0 0 0 1 3 4 1 1 0 0
OUTCOME
CURE
SURGICAL 10 6 6 4 1 8 3 9 2 2 3 1
DEATH
NON-SURGICAL 4 0 1 0 0 7 12 0 1 1 0 1
POST-OPERATIVE 4 3 0 0 0 5 0 4 3 0 2 1
AGE
AVERAGE 31 56 47 46 34 42 55 43 49 44 46 50
MEDIAN 30 61 40 52 34 42 56 42 50 45 43 44
RANGE 9-59 37-75 38-72 31-57 34 9-63 22-85 22-65 41-55 13-71 30-72 40-65
SEX
MALE 6 4 2 3 0 16 7 6 4 4 3 1
FEMALE 9 5 5 1 1 6 3 6 2 0 2 2
METASTASES 0 0 0 0 0 2 2 2 0 0 0 1
RECURRENCE 0 0 0 0 0 2 0 0 0 0 0 1

CHART I.—Symptomatology of small intestinal leiomyomata.

Acute intestinal obstruction[13] from intussusception or invagination occurred in 62% of the myomas located in the free-lying jejunum and ileum, but this does not occur in the duodenum which is retroperitoneal and fixed. The average age of these patients is conspicuously low in comparison with the other groups. Most of the tumors were less than 4 cm. in diameter, while the largest measured 12 cm. The only death in this group since 1910 occurred from bronchopneumonia a fortnight after resection. Recurrent acute or persistent partial obstruction[14] occurred in 7 patients over periods of months or years. Their average age is high.

All but one of the 7 cases of hemorrhage[16] experienced rather sudden weakness followed by the passage of copious tarry stools. Similar attacks recurred in 4 cases, and 6 were eventually cured by surgery. The seventh patient was hospitalized in a moribund condition from the exsanguination and soon succumbed. The tumor in these cases was usually less than 2 cm. in diameter and superficially ulcerated.

Newell and Rankin have emphasized the ulcer-like pain[15] which is produced by small submucosal myomas in the duodenum or jejunum. Only 1 of their 4 tumors exceeded 4 mm. in diameter.

The single instance of icterus[17] was cured by removal of a walnut-sized polypoid myoma lying just above the ampulla of Vater.

Outer leiomyomas are almost twice as frequent as the inner type. They tend to become much larger with increasingly conspicuous hemorrhagic cystic necrosis, and are often compared in size to a child's head. Spontaneous hemorrhage is the most common symptom and tends to persist or recur. Roentgenologic assistance in the diagnosis it not to be anticipated by conventional methods, since the barium meal is not impeded and the intestinal lumen is not distorted in any characteristic fashion.

The mechanism of hemorrhage[22] from outer leiomyomas is schematically presented in Chart II. Bleeding is rather rare in myomas of the duodenum, but appears in a preponderant number of those located in the jejunum and ileum. Only 6 of the 22 patients in this group were saved by surgical intervention. Five died of hemorrhage, 3 of pulmonary embolism (1 postoperative), and 2 of postoperative peritonitis.

Approximately 20% of the outer myomas were unexpectedly discovered at autopsy or laparotomy (asymptomatic[20]), in decided contrast to the inner leiomyomas. The 3 encountered at laparotomy for other reasons were successfully resected.

Thirteen patients had noted an abdominal mass[18] before they sought medical attention, although chronic digestive symptoms had been disregarded by most of them. Several of the tumors were "the size of a man's head," and central hemorrhagic necrosis was commonly mentioned in the descriptions.

Torsion or volvulus accounted for the cases of acute intestinal

obstruction,[19] while less clear-cut mechanical distortion presumably explains the more prolonged obstructive symptoms.[21]

The few cases tabulated under "indigestion"[23] include only those not properly classified elsewhere, and does not sufficiently emphasize the digestive symptoms which are commonly cited, *e. g.*, alter-

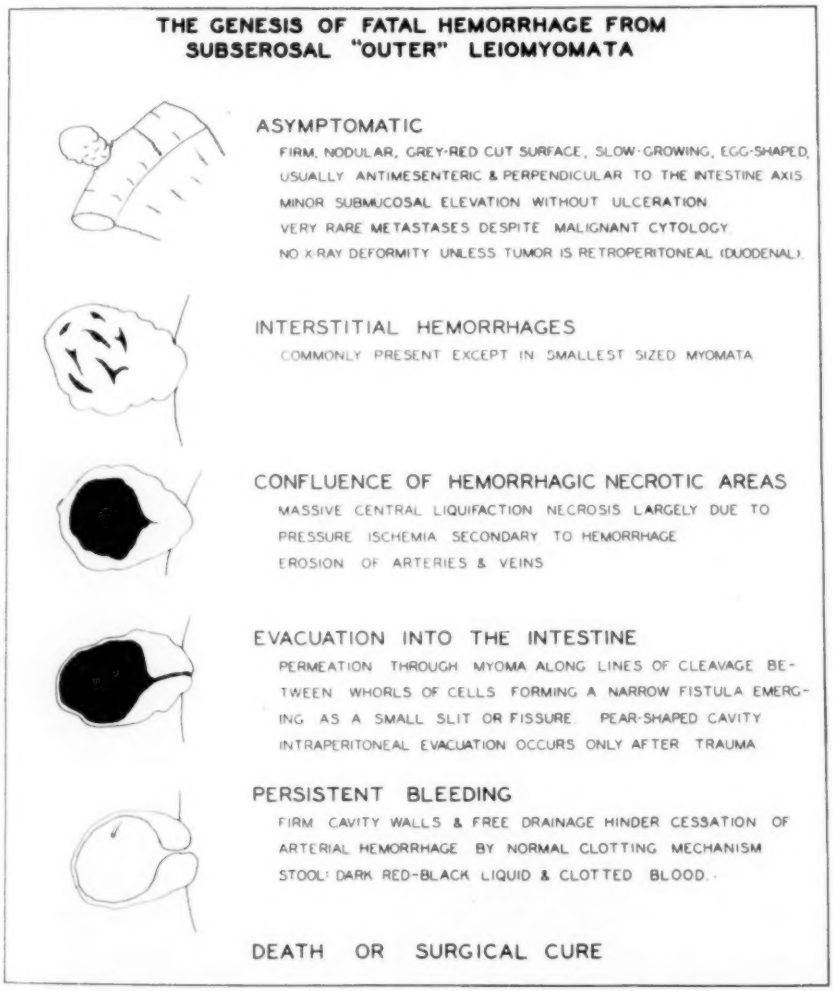
THE GENESIS OF FATAL HEMORRHAGE FROM SUBSEROSAL "OUTER" LEIOMYOMATA
ASYMPTOMATIC
FIRM, NODULAR, GREY-RED CUT SURFACE, SLOW-GROWING, EGG-SHAPED, USUALLY ANTIMESENTERIC & PERPENDICULAR TO THE INTESTINE AXIS
MINOR SUBMUCOSAL ELEVATION WITHOUT ULCERATION
VERY RARE METASTASES DESPITE MALIGNANT CYTOLOGY
NO X-RAY DEFORMITY UNLESS TUMOR IS RETROPERITONEAL (DUODENAL).
INTERSTITIAL HEMORRHAGES
COMMONLY PRESENT EXCEPT IN SMALLEST SIZED MYOMATA
CONFLUENCE OF HEMORRHAGIC NECROTIC AREAS
MASSIVE CENTRAL LIQUIFACTION NECROSIS LARGELY DUE TO PRESSURE ISCHEMIA SECONDARY TO HEMORRHAGE EROSION OF ARTERIES & VEINS
EVACUATION INTO THE INTESTINE
PERMEATION THROUGH MYOMA ALONG LINES OF CLEAVAGE BETWEEN WHORLS OF CELLS FORMING A NARROW FISTULA EMERGING AS A SMALL SLIT OR FISSURE. PEAR-SHAPED CAVITY
INTRAPERITONEAL EVACUATION OCCURS ONLY AFTER TRAUMA
PERSISTENT BLEEDING
FIRM CAVITY WALLS & FREE DRAINAGE HINDER CESSATION OF ARTERIAL HEMORRHAGE BY NORMAL CLOTTING MECHANISM
STOOL: DARK RED-BLACK LIQUID & CLOTTED BLOOD.
DEATH OR SURGICAL CURE

CHART II

nating diarrhea and constipation, abdominal discomfort or pain, a feeling of distention, gaseous eructation, and loss of appetite. In this group is included the first surgical cure of this condition (Babes and Nanu, 1897).

In 3 instances where the tumor reached quite large proportions,

rupture[24] of the necrotic areas into the peritoneal cavity occurred. One physician had the misfortune to have this occur during palpation of the cystic mass. This tumor was extirpated, recurred 5 years later, and was again successfully removed.

Summary. Myomas of the small intestine in general produce symptoms during middle age or later. Inner myomas tend to produce intestinal obstruction by intussusception, hemorrhage by superficial ulceration, or ulcer-like pain perhaps through traction stimulation of the mucosa. Outer myomas are particularly prone to dangerous hemorrhage, are frequently found unexpectedly at laparotomy or autopsy, may reach such size as to attract the patient's attention, and may by mechanical stress produce intestinal obstruction, more commonly partial than complete. As a rule, conventional Roentgen studies have not given material assistance in the diagnosis of this tumor, but the method of intestinal intubation together with radiologic examination (Abbott[1]) may prove helpful.

An instance of probably preventable death due to persistent hemorrhage from a small outer myoma of the ileum is reported, stressing the justification of exploratory laparotomy in patients whose persistent enterorrhagia does not seem explicable upon the basis of bleeding ulcer.

A schematic analysis of the symptomatology of this tumor is presented, based upon 109 recorded cases.

Conclusions. 1. Inner (submucosal) leiomyomas of the small intestine tend to remain small and commonly produce symptoms which lead to surgical intervention and a high percentage of cures. No metastases have been reported.

2. Outer (subserosal) leiomyomas grow much larger, frequently attracting the patient's attention through their size. Metastases or recurrence occurred in 16% of this group. Progressive central liquefaction necrosis in the tumor, with evacuation into the intestinal tract, produces a pseudodiverticulum from which, unless operation is performed, severe enterorrhagia is apt to continue until death.

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STUDIES OF MYOHEMOGLOBIN AT HIGH ALTITUDES.

By Alberto Hurtado, M.D.,
PROFESSOR OF PATHOLOGICAL PHYSIOLOGY; DIRECTOR OF THE RESEARCH LABORATORY,
Andrés Rotta, M.D.,
SENIOR ASSISTANT,
AND
César Merino, B.S. and Julio Pons, B.S.,
JUNIOR ASSISTANTS, FACULTY OF MEDICAL SCIENCES, LIMA, PERU.

(From the Research Laboratory and Department of Pathological Physiology, Faculty of Medical Sciences.)

The process of adaptation to a low barometric pressure has been a subject of interest to physiologists for a good century. In spite of numerous observations, however, we have not yet a precise knowledge of the basic mechanism which would explain the profound difference which exists between the newcomer and the native of the altitude. It seems to us that two main factors are responsible for the failure to disclose the fundamental aspect of the problem. First, is the constantly repeated attempt to interpret the changes which occur in men and animals during the first few days or weeks of residence at high altitude in terms of final adaptative processes; and, second, the relatively few investigations concerning the physiologic characteristics of men and animals who are born and raised in high places. It is unquestionable that only a thorough study of the latter will result in showing the mechanism or mechanisms, which are responsible for leading unrestricted physical and mental activities in a condition of constant anoxemia.

The important work of Whipple and his associates on muscle hemoglobin, to which we will make a detailed reference in the discussion of our findings, justifies assignment to this substance of an important rôle in muscle economy and work. The determination of this hemoglobin in animals (dogs) born and raised in high regions of the Peruvian Andes, and its possible significance from the point of view of adaptation to the altitude, has been the subject of the present investigation.

Material and Methods. For comparative purposes we selected 7 healthy adult dogs (Nos. 1 to 7) born and raised in Lima (sea level). These dogs were placed on a uniform diet (meat, potatoes and rice) for 8 weeks previous to the determination of muscle hemoglobin. A moderate degree of physical activity was allowed.

At high altitude we selected 7 other healthy adult dogs: 4 of these (Nos. 8 to 11) were born and raised in Morococha (at 14,890 feet with an average barometric pressure of 415 mm. Hg); and the last 3 (Nos. 12 to 14) were born and raised in Oroya (at 12,300 feet with an average barometric pressure of 485 mm. Hg). The dogs studied in Morococha were also placed on the same uniform diet for 8 weeks before the determination; those studied in Oroya were not subject to this previous observation.

The method followed was that of simultaneous bleeding and perfusion (Whipple[9]): the dog was placed under ether anesthesia, and by careful dis-

section of the neck one of the carotid arteries, and the external jugular vein on the opposite side, were exposed. Adequate cannulæ were inserted in these vessels and warm, freshly prepared Locke's solution, from a graduated bottle was allowed to enter by gravity into the vein. Simultaneous bleeding was started from the artery and the blood received in a graduated cylinder. In every case the inflow and outflow were regulated so that the difference between the two would not exceed 50 to 100 cc., thus avoiding edema of the tissues. When the respirations and heart contractions began to show evident weakening and irregularities a subcutaneous injection of 0.5 cc. adrenalin chloride was administered, in an effort to prolong the life of the dog as long as possible. The simultaneous perfusion and bleeding were carried on until the death of the dog; immediately after this the abdomen was opened and the vena cava cut. At the same time a moderate amount of Locke's solution was allowed to enter through the carotid artery and the perfusion continued for a short time, while the legs and trunk were massaged to expel the last traces of circulating blood. After this procedure the intestines, mesentery and lungs appeared macroscopically, in all cases, as being completely free of blood. In all determinations a hematocrit reading in the circulating arterial blood (using Wintrobe's hematocrit tube) was taken before the operation and just before death. In the dogs studied in Lima (sea level) the hematocrit figure *before* the operation averaged 47.4 % red cells; *afterwards* 1.1 % (variations between 0.5 and 1.6 %). These figures indicate a thorough elimination of practically all the circulating blood.

At high altitude, perfusion and bleeding were considerably more difficult on account of the higher initial hematocrit (which averaged 59.2 % red cells in the 7 dogs) and consequently increased viscosity of the blood. Considerable more fluid was used in the perfusion, and in a few instances we failed to carry on the determination on account of clotting of the blood in the cannulæ. In the 7 dogs which were finally studied the average hematocrit figure, after bleeding before death, was 2.4 % red cells; but in 4 this figure was less than 2 % (Fig. 1). It must be mentioned that this figure cannot be considered as an ultimate indication of the thoroughness of the removal of circulating blood, because in all experiments the perfusion and bleeding were carried on for some time after death.

A red cell count and hemoglobin determinations were also made in the sample of blood taken before perfusion was started. For the hemoglobin determination a Hellige hemometer, previously calibrated, was used.

A careful dissection of the muscles was performed immediately after the above procedures. For this purpose four different groups were selected: the adductors of the legs; the pectorals of the chest; the diaphragm and finally the heart. All the fat and fascia were removed as carefully as possible; the muscle was finely divided and cut, and portions of 10 gm. were very carefully weighed, using a sensitive scale. In all cases duplicate samples were obtained. The hemoglobin of the muscles was then extracted using a 0.4 % ammonium hydroxide solution, and this extraction carried out for 24 hours in the ice box. Then the extracts were filtered and changed to an acid hematin solution by the addition of concentrated HCl. For comparative purposes we used a similar solution of human blood, in which the hemoglobin content had been carefully determined, using the Van Slyke and McNeil[8] manometric method. The final comparison was made in a Duboscq colorimeter and the final figure represented the average of the figures obtained in the two samples.

Results. See Table 1 for changes in the peripheral blood. In the dogs observed at high altitude there is a considerable higher level of circulating red cells and hemoglobin, and also a greater proportion

of red cells to plasma. Thus we find an average increase of 1.85 millions red cells per c.mm. in this group of animals as compared with the ones studied at sea level, and there is also a correspondent increase of 6.3 gm. of Hb. per 100 cc. of blood and 11.8% red cells

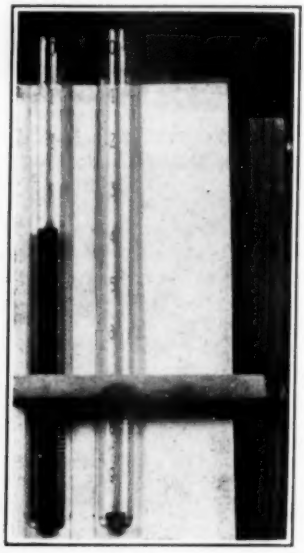

FIG. 1.—Dog 10, high altitude. Hematocrit determination (Wintrobe) in the circulating blood; 1, before simultaneous perfusion and bleeding was started and, 2, just before the death of the dog.

TABLE 1.—BLOOD VALUES IN THE OBSERVED DOGS.

(*Determinations made in the circulating blood.*)

		SEA LEVEL.				ALTITUDE.			
Dog No.	Wt. (kilo).	Red cells (mill. per mm.³).	Hemoglobin (gm. per 100 cc.).	Hematocrit % (red cells).	Dog No.	Wt. (kilo).	Red cells (mill. per mm.³).	Hemoglobin (gm. per 100 cc.).	Hematocrit % (red cells).
1	6.20	....	....	....	8	14.4	7.90	19.4	57.9
2	6.50	8.04	17.2	58.8	9	10.0	6.84	18.2	53.3
3	11.0	....	....	....	10	9.0	8.50	23.2	66.9
4	12.0	6.04	14.5	45.0	11	7.4	7.84	20.4	62.3
5	14.0	5.64	12.4	40.2	12	18.5	9.46	23.4	67.6
6	10.0	6.00	14.6	51.6	13	9.5	6.57	18.4	45.7
7	15.2	4.79	12.6	41.5	14	10.2	8.55	21.4	61.0
		Averages.					Averages.		
	10.7	6.10	14.3	47.4		11.3	7.95	20.6	59.2

(hematocrit). These findings in the circulating blood correspond to the well known polycythemia of altitude and its significance does not require further discussion in this paper.

The results obtained in the muscle hemoglobin determinations are summarized in Table 2, and in a graphic form in Fig. 2. Both at

sea level and at high altitude the diaphragm and leg muscles contain more hemoglobin than the chest and heart muscles, in the order given, and these results agree with the observations made by Whipple[9] a few years ago. At high altitude there is a well marked and decided increase in the hemoglobin content of the muscles. This

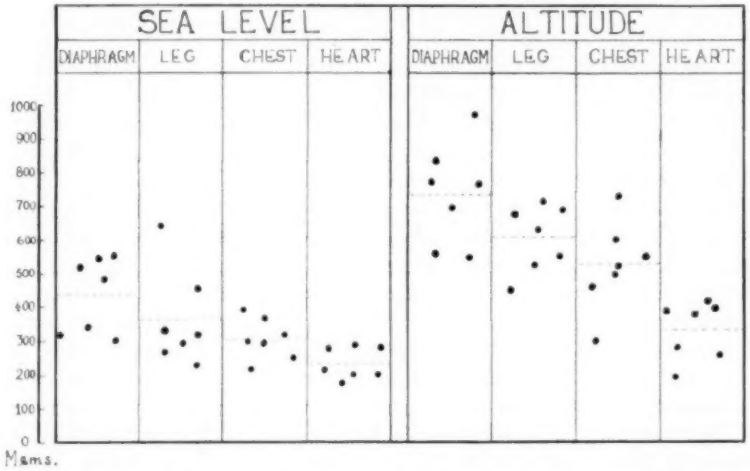

FIG. 2.—Determinations of myohemoglobin, expressed in mg. per 100 gm. of muscle, made in 7 dogs at sea level and in another 7 born and raised at high altitude. (Leg muscles: adductors; chest muscles: pectorals.) The dots correspond to the findings in each dog; the transverse lines represent the average value of all the determinations.

TABLE 2.—MILLIGRAMS OF MYOHEMOGLOBIN PER 100 GM. OF MUSCLE.

(Determinations made in 14 dogs.)

		Sea Level.						Altitude.			
Dog. No	Wt. (kilo).	Diaphragm.	Leg.	Chest.	Heart.	Dog No.	Wt. (kilo).	Diaphragm.	Leg.	Chest.	Heart.
		Mg. Hb. per 100 gm. muscle.						Mg. Hb. per 100 gm. muscle.			
1	6.2	321	294	296	206	8	14.4	696	532	499	285
2	6.5	483	320	322	220	9	10.0	560	451	463	256
3	11.0	520	453	394	296	10	9.0	549	557	302	194
4	12.0	340	273	224	204	11	7.4	764	688	551	415
5	14.0	301	232	252	174	12	18.5	837	712	604	377
6	10.0	552	643	372	277	13	9.5	966	679	723	399
7	15.2	547	337	299	285	14	10.2	771	632	525	395
		Averages.						Averages.			
	10.7	438	365	308	237		11.3	735	607	524	331

is more accentuated in the diaphragm, leg and chest which exhibit an increase of 66 to 70% of this substance, as compared with the same group of muscles at sea level. The heart has about 40% more hemoglobin at high altitude. It is significant to find that in all the dogs studied in Oroya and Morococha the content of hemoglobin in each muscle is higher than the correspondent average figure found

at sea level. It is also interesting to notice that the diaphragm, which is a muscle subjected to an intense work at high altitude on account of the more frequent and deeper respirations, contains comparatively more hemoglobin than the other muscles: thus in Lima the diaphragm contains 73, 130 and 201 more mg. of Hb. per 100 gm. than the leg, chest and heart respectively, while at high altitude it contains 128, 211 and 404 more mg.

Comparing the increase of hemoglobin in the blood and in the striated muscle, we find that the latter is more marked: the hemoglobin shows a gain of about 44% in the blood of the dogs living under the influence of a low barometric pressure, while the striated muscles of these animals have 66 to 70% more of this substance as compared with those living at sea level.

Discussion. Although numerous observations have been made at high altitude on circulating hemoglobin, we are not aware of any previous work on the hemoglobin content of the muscles. Investigators have always been attracted to the problems of oxygen acquisition at lung level and its blood transport, disregarding what it appears to be the most important and fundamental aspect of adaptation: the adequate supply of oxygen, which is carried at a low tension, to the tissues.

The work of Whipple and his associates[5, 6, 9, 10] has shown that the hemoglobin contained in the muscles is a stable substance, not subject to wide variations even in conditions of anemia and deficient diet intake, in contrast with the labile character of the circulating hemoglobin. They have also demonstrated that the amount of myohemoglobin depends in large extent on the degree of muscular exercise and activity. This fact suggests at once that this substance plays an important rôle in muscle economy and work, being perhaps concerned with a rapid gaseous interchange. The observations carried out in dogs were confirmed in studies made in human autopsy material; Woodruff and Whipple[11] concluded that in man, as in the dog, the concentration of hemoglobin within the muscle fibers is determined more by the degree of muscular activity than by the level of blood hemoglobin.

The above findings give a special interest to the investigation of the amount of hemoglobin contained in the muscle fibers of animals fully adapted to a condition of chronic anoxemia in the altitude. Do they also show an increase of this substance and in this way the acquisition of O_2 by the tissues is greatly facilitated in spite of the low tension at which this gas is held in the circulating blood? Our findings seem to warrant an affirmative answer, and several considerations indicate that it is highly probable that the fundamental mechanism of adaptation lies at *tissue level*. Hurtado,[4] in 1932, observed that although a large percentage of natives living in the Peruvian Andes exhibit supernormal circulating hemoglobin, there was a wide variation in this substance, and the degree of adaptation

had no relationship to its concentration. Guzmán Barrón, Dill, Edwards and Hurtado[3] have recently demonstrated that the occurrence of Soroche (mountain sickness) does not have any relationship to the degree of anoxemia in the arterial blood, the O_2 and CO_2 tension in the alveolar air, or to the amount of hemoglobin in the blood; and they concluded that it is probable that the tissue system of transporting O_2, of which the myohemoglobin is an important part, plays an important rôle in the mechanism of this syndrome. Dill, Edwards and Christensen[2] in the Chilean Andes failed to find any relationship between the degree of adaptation and the level of oxygen saturation in the arterial blood or the oxygen tension in the alveolar air.

The observations of Campbell[1] have special significance in this connection; this investigator found an elevated O_2 tension in the tissues of animals (rabbits) which showed a good adaptation to a low barometric pressure, in contrast with a low tension in those (cats, monkeys) which were poorly adapted to the abnormal environmental condition.

Clinically, there is a similarity between the symptoms found in Soroche and those of acute alcoholism, and Palthe[7] demonstrated that the latter condition is essentially due to a state of tissue (histotoxic) anoxemia.

The observations just mentioned emphasize the importance of considering adaptation in terms of mechanisms which operate at tissue level. Among these mechanisms it is likely that an increase of hemoglobin within the muscle fibers plays an important rôle and is perhaps one of the most fundamental adaptative processes in organism which are born and raised at high altitude, and which represents *adaptation* in its true significance.

Summary. Determinations of muscle hemoglobin by Whipple's method have been made in dogs born and raised at high altitude, and its results compared with similar observations made at sea level.

An increase of the hemoglobin content of the muscles has been found in the group of dogs at high altitude. It is suggested that this represents an important mechanism of adaptation to a condition of chronic anoxemia.

The senior author (A. H.) wishes to express his appreciation to Dr. G. H. Whipple for the kind personal demonstration of his method and the experience gained while working in his Department at the University of Rochester Medical School (1933).

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BOOK REVIEWS AND NOTICES.

THE TREATMENT OF DIABETES MELLITUS. By ELLIOTT P. JOSLIN, M.D. (HARVARD), M.A. (YALE), Medical Director, George F. Baker Clinic, New England Deaconess Hospital; Clinical Professor of Medicine, Harvard Medical School; Consulting Physician, Boston City Hospital. With the Coöperation of HOWARD F. ROOT, M.D., Physician, New England Deaconess Hospital; Instructor in Medicine, Harvard Medical School, PRISCILLA WHITE, M.D., Physician, New England Deaconess Hospital; Instructor in Pediatrics, Tufts College Medical School, and ALEXANDER MARBLE, M.D., Physician, New England Deaconess Hospital; Assistant in Medicine, Harvard Medical School. Pp. 707; 22 illustrations and 142 tables. Sixth Edition, thoroughly revised. Philadelphia: Lea & Febiger, 1937. Price, $7.00.

MADE necessary by the discovery of protamine insulin, the new sixth edition gives information on this valuable new method of treatment that is based on experience in over 1200 cases. The author's experience extending over 39 years and with over 15,000 cases, and his consummate skill in presenting his material in an impressive and interesting way, continue to make this book not only the standard work on Diabetes but also one of the outstanding medical texts in the English language. R. K.

THE NORMAL ENCEPHALOGRAM. By LEO M. DAVIDOFF, M.D., Assistant Professor of Neurology in the College of Physicians and Surgeons, Columbia University; Attending Neurological Surgeon to the Neurological Institute of New York, New York City, and CORNELIUS G. DYKE, M.D., Assistant Professor of Radiology in the College of Physicians and Surgeons, Columbia University; Assistant Director in the Department of Radiology of the Neurological Institute of New York, New York City. Pp. 224; 149 illustrations. Philadelphia: Lea & Febiger, 1937. Price, $5.50.

THIS monograph gathers together very well our knowledge of encephalography and encephalograms. The discussion of the technique of performing an encephalogram, the reactions that may follow the procedure and the means of counteracting them are fully detailed. The indications for and against the introduction of air by the lumbar route are considered. The shadows seen on the Roentgen ray film from air in the ventricles, the basilar cisternæ and the finer ramifications of the subarachnoid spaces are described and carefully correlated by good anatomical illustrations. Particularly important is the identification of air shadows seen in the basilar citernæ and the cortical sulci.

The Reviewer can find but one fault with this excellent monograph. A part of an encephalogram is illustrated and the details are described as normal. This is done thoroughly and no area is omitted. But there is no whole encephalographic outline, antero-posterior, postero-anterior, and right and left lateral which is given as a normal. Nothing is said of normal variations from an accepted standard, for no accepted standard of normality throughout the whole ventricular, cisternal and subarachnoid space is set up. Although this monograph is based upon a study of 4000 cases, presumably all of them had some intracranial abnormality, otherwise an encephalo-

gram would not have been done. While, therefore, normal details of all brain areas could be found in this series, a group of encephalograms normal in every way could not be presented. But it is exactly this that the medical profession needs. Encephalograms are being introduced as evidence in medico-legal cases. Physicians are being called upon to state whether certain encephalographic changes can be relied upon to indicate brain injury which might produce definite symptoms.

This monograph is important for it sets up normals in encephalographic shadow detail in local areas, whereby abnormalities presumably pathologic may be identified. But only too often apparent changes in an encephalogram are diffuse and widespread involving the entire ventricular system, the whole subarachnoid space and basilar cisternæ. Are such slight differences in the air shadows due to lesions or to "normal abnormalities"?

However, failure to describe an encephalogram normal in every detail is hardly a valid criticism of this excellent monograph. The information the Reviewer demands will not be forthcoming until some enterprising soul carries out 500 encephalograms on patients with no clinical evidence of an intracranial lesion. Then and then only shall we have knowledge of a completely normal encephalogram and the normal variations which can occur without specific cause. And what a blessing such information will be to an honest witness in attempting to evaluate the medico-legal worth of many encephalograms.

The publishers of this monograph are to be congratulated on the excellence of the reproduction of the Roentgen ray films and on the nearly complete lack of typographical errors. An excellent bibliography is appended.

This monograph can be recommended unqualifiedly as a basis for the interpretation of encephalograms. Every radiologist, neurologist and neurosurgeon who has to read them should study it carefully. F. G.

Heart Failure. By Arthur M. Fishberg, M.D., Associate in Medicine, Mount Sinai Hospital, New York City. Pp. 788; 25 illustrations. Philadelphia: Lea & Febiger, 1937. Price, $8.50.

The author states that his aim is to portray the advances in knowledge of the nature and treatment of circulatory failure, for the practising physician, in a fashion that will aid him in his daily work. The discussion is comprehensive and includes practically all aspects of circulatory failure, whether it originates in the heart or in the periphery. The literature has been carefully studied and utilized. The author has an excellent critical sense as well as an extensive knowledge of his subject and is able to distinguish between sound and unsound work. The book is unreservedly recommended to physicians who wish to bring their knowledge of the subject of circulatory failure up to date. C. W.

Family Care of Mental Patients. A Review of Systems of Family Care in America and Europe. Edited by Horatio M. Pollock, Ph.D., New York State Department of Mental Hygiene; with 5 Contributors. Pp. 247; 22 illustrations. Utica, N. Y.: State Hospital Press, 1936. Price, $2.50.

This collaborated study of the systems employed in Europe and the United States tells of a neglected phase of psychiatry. Most of those suited to this care are mental patients, although some epileptics and feebleminded can be farmed out; however, none may show violence, sex tendencies nor the urge to escape. The movement began at Gheel, Belgium in the

sixth century, where at present about half the town-families are hosts to some 3000 patients. The advantages to these colonists are home comfort, normal associations, greater freedom and work suited to their condition, some being self-supporting; to the foster families comes greater economic security; and since fewer institution buildings, with their expensive maintenance are required, the burden upon the taxpayer is lessened. In America, Massachusetts was pioneer in family care, with New York recently availing herself of its advantages. It is hoped that this country may see more and more mental patients cared for in homes. N. Y.

THE CURE OF HIGH BLOOD PRESSURE BY RESPIRATORY EXERCISES. By LOTHAR GOTTLIEB TIRALA, M.D., PH.D., Professor of Medicine, University of Munich. Authorized Translation, by FREDA DOUGLAS and ALBRECHT DOUGLAS, M.D., PH.D. Pp. 71; 11 illustrations and 2 colored plates. New York: B. Westermann Company, Inc., n.d. Price, $1.25.

THE author believes that in hypertension there is a state of chronic suffocation, the result of a decreased sensitivity of the respiratory center and consequent underventilation. The retained CO_2 as well as derivatives of ingested meat cause a stimulation of the vasoconstrictor center, bringing about hypertension. His treatment therefore stresses deep breathing exercises and a vegetable diet. Neither the argument nor the few illustrative case reports (less than a dozen) are convincing. The translation is as poor as the book. R. K.

THE BIOLOGY OF HUMAN CONFLICT. An Anatomy of Behavior, Individual and Social. By TRIGANT BURROW, M.D., PH.D., Scientific Director, The Lifwynn Foundation, New York City. Pp. 435. New York: The Macmillan Company, 1937. Price, $3.50.

ON Lake Chateaugay is Camp Lifwynn, where in a "normal asylum," a variant psychoanalyst and others work out their chosen problems. With a flair for doing unusual things, their leader, a "phyloanalyst," has established a laboratory for group-analysis, co-workers being lay and professional, normal and neurotic, male and female. Were it not for an informative glossary, this investigator would confound one with his Winchell-like urge for coining words.

Phyloanalysis (literally, not race-analysis but group-analysis) is concerned with the dissection of group-behavior disorders; a neurosis is regarded as an internal tensional affection enveloping mankind, and its correction calls for a "basic physiological reorientation of the total organism in relation to the total environment."

Psychoanalysis tends toward mysticism and its votaries are too dogmatic. But perhaps this writer is ahead of his time, a calamity that has overtaken others—Socrates, Bruno, Columbus, Bacon, Galileo. Further findings of this movement may be sponsored by the Foundation. N. Y.

PHYSICIAN, PASTOR AND PATIENT. Problems in Pastoral Medicine. By GEORGE W. JACOBY, Past President of the American Neurological Association and the New York Neurological Society. Pp. 390; 20 illustrations. New York: Paul B. Hoeber, Inc., 1936. Price, $3.50.

IN view of the lessening opportunities of the physician for a close personal relationship to his patients, the author points out that the physician can find in the clergyman a valuable ally in the handling of many medical and

social problems. He cites many ways in which religion in the past and present has directly influenced the health problems of mankind. He is interested in the religions of today insofar as they affect public health and physical well-being. "Faith and doctrine do not enter into discussion except when they bring physician and clergyman into harmony or conflict." The author deals with numerous practical problems, such as contraception and abortion, suicide, the divorce problem, crime, sterilization, sex education, euthanasia, in a calm and fair manner, with statements of opinions on these subjects as held by the adherents of various faiths. The book will be found interesting and useful by physicians and clergy alike.

R. K.

CANCER AND DIET. With Facts and Observations on Related Subjects. By FREDERICK L. HOFFMAN, LL.D., the Biochemical Research Foundation of the Franklin Institute, Philadelphia. Pp. 767; 187 tables and 8 charts. Baltimore: The Williams & Wilkins Company, 1937. Price, $5.00.

THE material in this unique volume is considered under four separate headings: 1, Dietary Theories of Cancer; 2, The Modern Diet; 3, Cancer Metabolism; 4, Dietary Facts Concerning Cancer Patients. The discussion is exhaustive. While it is true that much of the material is worthless as scientific data, it helps one appreciate the long and tedious search that has gone before.

The evidence presented throughout the book is more or less conflicting. Almost every question involves contradictions and divergencies of opinion. One cannot help being amazed, however, at the quantity of data gathered for this analysis. Such items as race, religion, smoking, water, and vitamin intake, and their relation to cancer are meticulously presented.

We can think of nothing that might have added to the all-inclusive character of this review. Yet, in spit of the excellence of the presentation, we could not convince ourselves that diet was a dominating factor in cancer.

P. H.

A TEXTBOOK OF MEDICINE. By CHARLES PHILLIPS EMERSON, M.D., Research Professor of Medicine, Indiana University; Formerly Associate in Medicine and Medical Resident, Johns Hopkins University and Hospital, etc. Pp. 1296. Philadelphia: J. B. Lippincott Company, 1936. Price, $8.00.

THIS new medical text has a number of interesting features. Chief of these is the author's aim to present Internal Medicine "in terms of the clinical pictures of diseases, and to explain these by the findings of pathology, biochemistry, and the other preclinical sciences, rather than to emphasize the latter." The author therefore portrays the syndrome which each disease presents, and, "lest they blur this, has added the contributions of the preclinical sciences (and more extensively than is the custom) in special paragraphs and footnotes." Another feature is the numerous historical references and the short biographies of many of the pathfinders in medicine. Emphasis is also placed on the personal factor in disease, including heredity, environment and the patient's biological and emotional reactions. The book, which is very well written, is obviously the product of a wise and seasoned clinician. It is open to less than average of the objections which so often apply to a textbook of medicine by a single author, who can obviously not be an authority on all phases of internal medicine and who is bound to have a few peculiarities of opinion. Thus one might criticize the understatement of the value of Roentgen rays in pulmonary tuberculosis;

the overcautious, at times antagonistic, attitude toward allergy and the denial of the possibility of an allergic factor in migraine (yet the book contains more and better information on allergy than do most one-volume textbooks of medicine); the failure to mention ergotamine tartrate in the treatment of the migranous paroxysm and prostigmine for myasthenia gravis. The typesetter slipped in an error by putting "severe" instead of "swine" before influenza in connection with Shope's work. All of these are points which can easily be taken care of in future editions. The fact remains, that the book reached a high standard of excellence and should be welcomed by teachers and students alike. R. K.

EPIDEMIOLOGIE. Grundbegriffe und Ergebnisse. By PROF. DR. MED. ADOLF GOTTSTEIN, Ministerial-Direktor i. R., Berlin. Pp. 285; 16 figures. Wien: Franz Deuticke, 1937. Price, Paper, M. 15; Bound, M. 17.40.

THIS book has been written by an experienced worker who looks back on a long and successful career as an epidemiologist. There is a thorough discussion of the causes, courses and sequels of individual epidemics. However, the most valuable ingredient of the book appears to be a critical analysis to which the fundamental principles of epidemiology are subjected. W. E.

THE INTERNATIONAL MEDICAL ANNUAL. Fifty-fifth Year, 1937. A Yearbook of Treatment and Practitioner's Index. Thirty-four Contributors. Editors: H. LETHEBY TIDY, M.A., M.D. (OXON.), F.R.C.P., and A. RENDLE SHORT, M.D., B.S., B.Sc., F.R.C.S. Pp. 605; 89 text illustrations and 68 plates (some in color). Baltimore: William Wood & Co., 1937. Price, $6.00.

As usual, this annual presents an authoritative and reliable survey of recent progress in medicine—the word being interpreted in a wide sense. While great skill has been shown in condensing the huge material into usable form, the editors have wisely left the contributors free to select without insisting on the impossible element of comprehensiveness. Without in any way, then, replacing textbooks or periodicals on the wide field covered, this annual should be of great use to the practicing physician in keeping him up to date, and as a desk companion. E. K.

THE TECHNIC OF LOCAL ANESTHESIA. By ARTHUR E. HERTZLER, A.M., M.D., PH.D., LL.D., F.A.C.S., Professor of Surgery in the University of Kansas; Surgeon to the Halstead Hospital, Halstead, Kansas, etc. Pp. 284; 142 illustrations. Sixth Edition. St. Louis: The C. V. Mosby Company, 1937. Price, $5.00.

THE sixth edition of Hertzler's book on local anesthesia has been changed very little from the fifth edition. Except for a few changes on spinal anesthesia and a few notations concerning the newer anesthetic drugs, the new edition has little to add over the previous one. The technique of local anesthesia is considered from the point of view of infiltration and local field block rather than regional or nerve block, so that the reader hunts in vain for the technique of the more complicated block, such as that of the brachial plexus. Anesthesia is described under regional sections and the book is well illustrated to show how the author induces his local anesthesia. The continued issuing of new editions of this work is a testimonial to its popularity. L. F.

CONTRIBUTIONS TO THE MICROSCOPIC ANATOMY OF THE PANCREAS BY PAUL LANGERHANS [Berlin, 1869]. Reprint of the German Original with an English Translation and an Introductory Essay by H. MORRISON, M.D. Pp. 39; illustrated. Baltimore: The Johns Hopkins Press, 1937 Price, $1.00.

AGAIN we are indebted to the Johns Hopkins Press for another interesting reprint of a medical classic. Morrison's Introductory Essay, list of publications, and three scarce photographs add to the value of this contribution to medical history. E. K.

MICROMETHODIK. Quantitative Bestimmung der Harn-, Blut- und Organbestandteile in kleinen Mengen für klinische und experimentelle Zwecke. By LUDWIG PINCUSSEN. Pp. 193; 31 illustrations. Sixth Edition. Leipzig: Franz Deuticke, 1937. Price, M. 5.

THIS manual describes procedures for the chemical analyses of the various components in the blood, urine, and other biological fluids such as may be presented to the biochemistry division of a hospital laboratory for analysis. For many of the analyses the author has selected and outlined only one method. Although the book mentions the principles upon which given analytical procedures are based, nevertheless, it contains very little critical evaluation of the methods. The bibliography is wholly unsatisfactory and the references, when given, are frequently incomplete. F. S.

THE PATIENT AND THE WEATHER. Vol. IV. Part 1. Organic Disease, Cardio-vascular-renal Disease. By WILLIAM F. PETERSEN, M.D. With the assistance of MARGARET E. MILLIKEN, S.M. Including a chapter on Experimental Endocarditis by ALEXANDER J. NEDZEL, M.D., Associate Professor in the Department of Pathology, Bacteriology and Public Health; University of Illinois, College of Medicine, Chicago. Pp. 663 (lithographed); 443 illustrations. Ann Arbor: Edwards Brothers, Inc., 1937. Price, $10.00.

IN the preceding volumes, were introductory chapters that analyzed pertinent topics. Here, everyday clinical episodes as observed in case reports are given immediate attention, with the primary interest, not in the end result, but in the fact, "that organic disease may take its origin from subminimal environmental stimuli." In Chapter I, a bit of spoofing is indulged in at the expense of the author's surgical and psychoanalytical friends. Chapter II, discusses March episodes. Chapters III, IV, V and VI, consider diseases of the heart, vessels and kidneys. Chapter VII, endocarditis, with Section A, discussing clinical cases; in Section B, are submitted various case histories from the service of colleagues, wherefrom, deductions were such that the attempt experimentally to produce lesions was decided upon. The final chapter by Professor Nedzel, assays the data obtained through experimental production of bacterial endocarditis in dogs. Here, following pressor episodes and bacterial injections, typical valvular endocarditis was produced, more readily so during late winter and spring. With the artificial production of pressor episodes, an occasional typical endocarditis was observed, without bacterial injections. Therefore, it is concluded that the thesis proposed by Petersen is experimentally demonstrable. Throughout the volume the research work is so intricate that it can only be appreciated by specialists. The bibliography is noteworthily extensive.
N. Y.

PHYSICIANS AND MEDICAL CARE. By ESTHER LUCILE BROWN, Department of Statistics, Russell Sage Foundation. Pp. 202. New York: Russell Sage Foundation, 1937. Price, 75c.

THE changes in the relation of medicine to society are taking place so rapidly and in so many ways that it is difficult for the members of the profession to realize their extent and significance. Therefore this book should have particular interest to those who wish to understand the present status of medicine and its changing position as a unit of our complex social structure. It indicates the modern trends and social forces affecting medical care and their influence on the profession.

The book is based on the more important literature which has recently appeared related to medical education and medical care, and is a fair-minded, clear summary of these voluminous writings which should be welcomed by the members of the profession who wish to know what is taking place in the American medical profession. It should also be of especial interest to those contemplating the study of medicine.

The problems of medical education are first discussed, followed by an account of the national organizations which guide and control the profession from within. The latter half of the book discusses the number of physicians and the demand for their services, the distribution of physicians and their incomes, new forms of medical service and finally the fundamental problem of adequate medical care for all the people. It is pointed out that serious difficulties confront those who seek to devise means for extending medical care to the entire population while still preserving all that is best in medicine, and the author indicates what these difficulties are. During the past few decades the problem in this country has been the improvement of medical education and the development of the basic sciences of medicine, while today the urgent problem "is that of devising ways and means whereby adequate care can be provided for the entire population and physicians compensated fairly for the service rendered." As this is primarily an economic problem involving both physicians and society in general, it is desirable for physicians to understand the demands of society upon medicine and for the laity to comprehend the needs, structure and functions of the medical profession.

This book should serve a useful purpose in stimulating a mutual understanding between the medical profession and the public, and the author is to be congratulated upon the presentation of a clear, concise and very interesting account of the present status of the medical profession in relation to the problem of the provision of medical care. G. R.

MATERNAL CARE. The Principles of Antepartum, Intrapartum, and Postpartum Care for the Practitioner of Obstetrics. Approved by The American Committee on Maternal Welfare, Inc. Prepared by DRS. W. C. DANFORTH, G. W. KOSMAK, R. L. DE NORMANDIE and F. L. ADAIR. DR. FRED. L. ADAIR, Editor. Pp. 93. Chicago: The University of Chicago Press, 1937. Price, $1.00.

THE widespread campaign for the improvement of Maternal Care showed a need for the concise statement of the principles of antepartum, intrapartum and postpartum care. It is felt that this handbook will amply supply the needs of the average practitioner of obstetrics. The material is simply and directly presented with emphasis on the cardinal principles and insistence on the nearest approach to asepsis which is possible and a short and direct discussion of obstetric operations and complications. It is hoped that the book will have a wide distribution among general practitioners, hospital interns, and public health nurses. P. W.

INFANTILE PARALYSIS AND CEREBRAL DIPLEGIA. Methods Used for the Restoration of Function. By ELIZABETH KENNY. With a Foreword by HERBERT J. WILKINSON, Professor of Anatomy and Dean of the Faculty of Medicine, University of Queensland. Pp. 125; 51 illustrations. Sidney, Australia: Angus & Robertson, Limited, 1937. Price, £ 1/1/–

THIS offering is of Sister Kenny's 16 years scientific work with patients, always under the care of medical men, wherein improvement was brought about in abandoned paralytics, some of 20 or 30 years standing; and more rapid improvement in early subjects, in whom active or passive movements of the joints, were made sometimes from the beginning. Patients were treated individually and alone; the position assumed was that most favorable to concentration, after which the subject was taught to visualize the area where muscle movements were expected. Believing she has a missio,n this woman endowed with an exceptional personality, boundless optimism and great physical energy, has been able to get some surprisingly brilliant results. Criticism is of neglecting to employ other useful methods such as massage and immobilization, which latter is for the most part condemned.

N. Y.

FISCHERISMS. Being a sheaf of sundry and divers utterances culled from the lectures of MARTIN H. FISCHER, Professor of Physiology in the University of Cincinnati. By HOWARD FABING. Pp. 47; 1 illustration. A Second and Enlarged Edition by Ray Marr. Springfield, Ill.: Charles C Thomas, 1937. Price, $1.50.

A PRIVATE print for Dr. Martin Fischer's students, this little anthology of aphorisms is, as stated on the cover, not for general circulation. Nevertheless, these asides from lectures on physiology contain not a few nuggets that are worth preservation as well as serving Cincinnati graduates as a "reminder of pleasant days gone by." The medical aphorism, as old as Hippocrates, has its appropriateness in these pithy, disjointed days, but also its limitations. As might be expected from a compilation of jottings from student note book margins, the levels vary greatly, nor are all the statements true or to be accepted—in some cases even the meaning is obscured by the syncopated form. However, many homely truths—piquantly expressed—may be found here applied to politics, philosophy and religion, as well as to all branches of medicine.

E. K.

A TEXTBOOK OF SURGICAL NURSING. By HENRY S. BROOKES, JR., M.D., Instructor in Clinical Surgery, Washington University School of Medicine; Surgeon to the Outpatients, Washington University Dispensary; Assistant Surgeon to Barnes Hospital. Pp. 636; 233 illustrations. St. Louis: The C. V. Mosby Company, 1937. Price, $3.50.

THE author, in conjunction with several nursing supervisors at the Barnes Hospital, has compiled a book of nursing for surgical nurses which describes fairly closely the procedures as followed at that hospital.

The book gives a short introduction describing inflammations and infections, wounds, bandages, first aid, pre- and postoperative care and, very briefly, anesthesia. The section on the operating room is good. The instrument set-ups for various operations are given in detail and one of the especially interesting parts of the book are the illustrations with names of the instruments used in various operations. There are sections on regional surgery and finally a chapter on postoperative complications and one describing the various procedures such as catheterization, intravenous glucose, etc. At the end is appended a glossary of words used in surgery, which are defined in relatively simple terms.

The book is well illustrated throughout. Many of the illustrations have been borrowed from the works of other authors and some of them, as for

instance the illustration on page 113, have lost a great deal of their sharpness in reproduction so that it is very difficult to see what is described in the plate.

If there is any criticism to be offered of the book it is that there is relatively little concerning the nursing care of surgical patients. Too much emphasis has been placed on the surgical procedures themselves so that the book is more suitable as an introduction to surgery for medical students than as a reference or textbook for nurses, whose education neither fits them nor whose duty makes it necessary for them to follow in intricate detail the technique of surgical operations. L. F.

PUBLIC MEDICAL SERVICES. A Survey of Tax-supported Medical Care in the United States. By MICHAEL M. DAVIS. Pp. 170. Chicago: The University of Chicago Press, 1937. Price $1.50.

IN the discussion of medical care in this country which is so active today, the term "state medicine" is frequently heard. It is sometimes called erroneously "socialized medicine," and is seldom defined by those who advocate or condemn its adoption as a solution for the problems of medical care. Although everyone who speaks of state medicine has in mind medical care furnished by the government and therefore supported by taxation, few have stopped to say whether the term includes all medical care, curative as well as preventive, or whether it applies only to certain medical functions and to certain groups of people. Does state medicine mean that government shall actually control medical service, or only help to pay for the needed medical care which individuals cannot or will not pay for?

Before anyone makes public utterances about the dangers and demoralization of state medicine or advocates it as a panacea, he should know its present status in this country, how it has developed, what medical services are now tax-supported and what its future is likely to be, as judged by the evolutionary processes now going on which are extending the scope of state medicine.

Michael Davis gives a clear and authoritative account of this subject. His book is an expansion and modification of the section on public medical services which he contributed to the report on health security, prepared for President Roosevelt's Committee on Economic Security in 1934. The first part of the book gives an account of the kinds and extent of medical service which are now supported by taxation in this country. The subject is described under such headings as: home medical care; hospitals for acute and chronic diseases; hospitals and clinics for mental disease and tuberculosis; tax payments to non-governmental hospitals; general medical care for certain non-dependent groups for whom special responsibility is assumed by a government agency; medical care for diseases or conditions of public health interest.

The second part of the book consists of Summary and Comments, emphasis being laid on quality of service and coördination of service. Evidence is presented which shows that over a quarter of the medical care furnished to wage-earners and other people with small or no incomes, constituting 85% of the population, is tax-supported at the present time.

The author emphasizes the importance of maintaining personal understanding and confidence between physician and patient as a fundamental element of effective medical service, and he points out that the medical profession must give intellectual effort to the dispassionate solution of the problems of professional service. The author also puts his finger on some problems of medicine requiring coöperation of service for their solution which should be given careful consideration by the profession.

Michael Davis is one of the best informed and most experienced students of American Medicine, as a service and as a profession. Although outside

of the profession, he has been integrated with it as an administrator for so many years that he may now be said to be one of our most valuable medical statesmen. His study of Public Medical Services is a clear and useful contribution to the knowledge which is beginning to answer some of the controversial questions regarding the medical care of the American people.

G. R.

AUTONOMIC NEURO-EFFECTOR SYSTEMS. By WALTER B. CANNON, George Higginson Professor of Physiology, Harvard University, and ARTURO ROSENBLUETH, Assistant Professor of Physiology, Harvard University. Pp. 229; 42 illustrations. New York: The Macmillan Company, 1937. Price, $4.00.

THIS monograph deals with "recently acquired evidence regarding the chemical step which intervenes between the nerve impulse and the effector in the functioning of the autonomic nervous system—not only the processes in the junctional region but also those occurring in the effectors themselves" (quotation from the authors' preface). It begins with a general consideration of the structure and functions of the autonomic nervous system, takes up some pertinent details of the finer innervation of smooth muscle, heart muscle, and glands, and proceeds to sketch the development of the current conception of transmission of nerve impulses by chemical agents liberated by the impulses—the so-called "cholinergic" and "adrenergic" conceptions; the first three chapters cover these points. Two chapters are then devoted to the parasympathomimetic substance (acetyl choline). The remaining nine chapters deal for the most part with the sympathomimetic substance ("sympathin") and with drug actions which bear upon it. The bibliography comprises 344 titles.

For the physician or biologist who desires a compact summary of reasons for believing that nerve impulses may be chemically transmitted, and a glimpse of some of the current conceptions of the ways in which chemical agents act upon living tissues so as to modify their function, this book is recommended most highly. Like nearly all recent monographs on this subject, this one makes the case for humoral transmission as strong as possible and the story is an extremely attractive one. Unlike the others, this one devotes more attention to "sympathin" than to acetyl choline; this is eminently fitting because the authors have done much more experimentation with the former than with the latter. Unfortunately "sympathin," being a substance of unknown composition (as the authors are careful to state), cannot be handled with the precision which has characterized the recent experiments made by Dale and his co-workers with acetyl choline; this precision furnishes the most potent argument in favor of humoral transmission, and one might expect the authors to include more of the cholinergic story for that reason, if for no other. Although the authors state (p. 123) that electrical phenomena in smooth muscle may be concomitants, not necessary links, in the excitatory chain, and that (p. 157) "sympathin" may be liberated in intimate relation to the reacting substance and this nerve stimulation may be effective after piperidinomethylbenzodioxane ("933 F") though a physiologically similar agent (adrenalin) injected into the blood is ineffective, they do not mention the converse possibility, namely that the liberation of "sympathin" may be only an incident in the excitatory process and the substance which reaches the blood stream may have had nothing to do with the physiologic effects of sympathetic nerve stimulation. The subject of humoral transmission of nerve impulses has developed too rapidly to permit impartial evaluation. Perhaps a few years hence the authors will revise or rewrite this monograph; comparison of the second edition with the first will be extremely interesting.

C. S.

HANDBOOK OF ORTHOPÆDIC SURGERY. By ALFRED RIVES SHANDS, JR., B.A., M.D., Associate Professor of Surgery in Charge of Orthopædic Surgery, Duke University School of Medicine, and Chief of the Orthopædic Service, Duke Hospital, Durham, N. C., etc. In Collaboration with RICHARD BEVERLY RANEY, B.A., M.D., Instructor in Orthopædic Surgery, Duke University, School of Medicine. Pp. 593; 169 illustrations. St. Louis: The C. V. Mosby Company, 1937. Price, $5.00.

DR. SHANDS in his "Handbook of Orthopædic Surgery" has presented the subject in a very clear and concise manner. It is easy to read, and the reader is not lost or confused by long statistical reports. The book is unique in that not only the author's opinion is expressed, but also that of many other leading orthopædic surgeons on the various subjects under discussion. The author has presented the fundamentals of Orthopædic Surgery, paying particular attention to diagnosis and treatment.

There are 169 illustrations, very well done, which help the reader to visualize their characteristic features.

The bibliography is carefully indexed and most complete, which should be of immense value to both students and practitioners of medicine inasmuch as the references include leading American and English authors.

T. O.

NEW BOOKS.

Human Understanding and Its World. A Study of Societies. By K. W. MONSARRAT, Consulting Surgeon, Northern Hospital, Liverpool; Formerly Dean of the Faculty of Medicine, University of Liverpool. Pp. 480; 42 figures. Liverpool: The University Press; London: Hodder & Stoughton, Ltd., 1937. Price, 15/–.

Russian Medicine. (Vol. XX of Clio Medica). By W. HORSLEY GANTT, M.D., Johns Hopkins University School of Medicine; Formerly Chief of Medical Division, American Relief Administration, Leningrad Unit (1922–1923); Collaborator in Pavlov's Laboratories (1925–1929). Pp. 214; 12 illustrations. New York: Paul B. Hoeber, Inc., 1937. Price, $2.50.

Practical Talks on Kidney Disease. By EDWARD WEISS, M.D., Professor of Clinical Medicine, Temple University School of Medicine, Philadelphia. Pp. 176; illustrated. Springfield, Ill.: Charles C Thomas, 1937. Price, $3.00.

Atlas of Hematology. By EDWIN E. OSGOOD, M.A., M.D., Assistant Professor of Medicine and Head of Experimental Medicine, University of Oregon Medical School, Portland, and CLARICE M. ASHWORTH, Medical Illustrator, University of Oregon Medical School, Portland. Pp. 255; 325 illustrations and frontispiece, all in full color. San Francisco: J. W. Stacey, Inc., 1937. Price, $10.00.

A Text-book of Medical Bacteriology. By R. W. FAIRBROTHER, D.Sc., M.D., M.R.C.P., Lecturer in Bacteriology, University of Manchester; Late Research Fellow in Bacteriology, Lister Institute, London. Pp. 437; 12 illustrations and 32 tables. St. Louis: The C. V. Mosby Company, 1937. Price, $4.50.

Family Care of Mental Patients. A Review of Systems of Family Care in America and Europe. Edited by HORATIO M. POLLOCK, PH.D., New York State Department of Mental Hygiene, Albany, N. Y. Contributors: EDGAR A. DOLL, PH.D., The Training School at Vineland, N. J.; HARRY A. LABURT, M.D., Harlem Valley State Hospital, Wingdale, N. Y.; PHILIP SMITH, M.D., New York State Department of Mental Hygiene, New York City; CHARLES E. THOMPSON, M.D., Gardner State Hospital, East Gardner, Mass.; CHARLES L. VAUX, M.D., Newark State School, Newark, N. J. Pp. 247; illustrated. Utica, N. Y.: State Hospitals Press, 1936. Price, $2.50. (For Review, see p. 715.)

Syphilis. The Next Great Plague to Go. By MORRIS FISHBEIN, M.D. Pp. 70; illustrated. Philadelphia: David McKay Company, 1937. Price, $1.00.

The British Encyclopædia of Medical Practice. Volume 4. Diarrhœa to Endoscopy of the Rectum. Under the General Editorship of SIR HUMPHRY ROLLESTON, BT., G.C.V.O., K.C.B., M.D., D.Sc., D.C.L., LL.D., Emeritus Regius Professor of Physic, Cambridge, etc. With the assistance in a consultative capacity of F. R. FRASER, M.D., F.R.C.P., G. GREY TURNER, D.Ch., M.S., F.R.C.S., JAMES YOUNG, D.S.O., M.D., F.R.C.S. Ed., F.C.O.G., SIR LEONARD ROGERS, K.C.S.I., M.D., LL.D., F.R.C.P., F.R.C.S., F.R.S. and F. M. R. WALSHE, O.B.E., M.D., D.Sc., F.R.C.P. Pp. 650; 129 illustrations. London: Butterworth & Co. (Publishers), Ltd., 1937. Price, $12.00.

Clinical Urinalysis and Its Interpretation. By ROBERT A. KILDUFFE, A.M., M.D., F.A.S.C.P., Director of Laboratories, Atlantic City Hospital; Pathologist, Atlantic County Hospital for Tuberculous Diseases; Serologist, County Hospital for Mental Diseases; City Bacteriologist, City of Atlantic City, etc. Pp. 428; 40 illustrations. Philadelphia: F. A. Davis Company, 1937.

Le Anemie Emolitiche Costituzionali Ereditarie. By DR. GIULIO MOMIGLIANO-LEVI. Pp. 108; 16 illustrations. Torino: Edizioni Minerva Medica, S. A., 1937. (Price not given.)

An Epiphyseal Chart. (Reprinted from an article published in The American Journal of Roentgenology and Radium Therapy, Vol. 30, No. 6, December, 1933.) By PAUL C. HODGES, PH.D., M.D., Division of Roentgenology, University of Chicago. Chicago: The University of Chicago Press, 1937. Price, 25c.

This chart makes available at a glance the developmental history of the bones of the human skeleton from fetal life to maturity. P.H.

International Clinics, Vol. III, Forty-seventh Series, 1937. Edited by LOUIS HAMMAN, M.D., Visiting Physician, Johns Hopkins Hospital, Baltimore, with 13 collaborators. Pp. 328; illustrated. Philadelphia: J. B. Lippincott Company, 1937.

This volume is made up of 24 articles covering many phases of medicine. It has an unusually distinguished list of contributors from several states but none from abroad. Conspicuous are the 9 articles from the Johns Hopkins Hospital.

Erbkrankheit und Fertilität. Mikropathologie der Spermien erbkranker Männer. By DR. med. et med. vet. H. STIASNY, Assistent der chirurgischen Abteilung des städtischen Krankenhauses "Am Urban," Berlin, and DR. med. K. D. J. GENERALES, JR., Lowell, Mass., z. Zt. Volontärassistent der chirurgischen Abteilung des städtischen Krankenhauses "Am Urban," Berlin. Mit einem Geleitwort VON PROF. DR. ERWIN GOHRBANDT. Pp. 163; 60 illustrations; 21 tables (16 in colors). Stuttgart: Ferdinand Enke, 1937. Price, Paper, Rm. 27.; Bound, Rm. 29.

Heilkunde und Volkstum auf Bali. By DR. med. WOLFGANG WECK, ehem. Hoofd-Gouvernementsarzt in Niederländisch-Indien. Pp. 248; 27 illustrations. Stuttgart: Ferdinand Enke, 1937. Price, Paper, Rm. 19; Bound, Rm. 20.60.

Recent Advances in Industrial Hygiene and Medicine. By T. M. LING, M.A., B.M. (OXON.), M.R.C.P. (LOND.), Senior Medical Officer, Bristol Police, etc. Foreword by J. A. NIXON, C.M.G., M.D., F.R.C.P., Emeritus Professor of Medicine, University of Bristol, etc. Pp. 212; 29 illustrations. Philadelphia: P. Blakiston's Son & Co., Inc., 1937. Price, $3.50.

The Patient and the Weather, Vol. IV, Part 2. Organic Disease. Hypo- and Hyperthyroidism, Diabetes, The Blood Dyscrasias, Tuberculosis. By WILLIAM F. PETERSEN, M.D., with the assistance of MARGARET E. MILLIKEN, S. M. Pp. 729 (lithoprinted); 380 illustrations. Ann Arbor: Edwards Brothers, Inc., 1937. Price, $11.00.

Injection Treatment of Hernia. By CARL O. RICE, M.D., F.A.C.S., Instructor in Surgery, University of Minnesota School of Medicine; Surgeon in Charge of the Surgical Out-Patient Department of Minneapolis General Hospital, etc. With the assistance and coöperation of HAMLIN MATTSON, M.D. Pp. 266; 83 illustrations. Philadelphia: F. A. Davis Company, 1937. Price, $4.50.

NEW EDITIONS.

Recent Advances in Pulmonary Tuberculosis. By L. S. T. BURRELL, M.A., M.D. (CANTAB.), F.R.C.P. (LOND.), Senior Physician to Royal Free Hospital; Physician to Brompton Hospital for Consumption and Diseases of the Chest, etc. Pp. 320; 22 text figures and 48 plates. Third Edition. Philadelphia: P. Blakiston's Son & Co., Inc., 1937. Price, $5.00.

Clinical Electrocardiography. By SIR THOMAS LEWIS, M.D., F.R.S., D.Sc., LL.D., F.R.C.P., C.B.E., Physician in charge of Department of Clinical Research, University College Hospital, etc. Pp. 128; 109 illustrations. Sixth Edition. London: Shaw & Sons Ltd., 1937. Price, 8s. 6d.

The continued popularity of this excellent little book and its reasonable price are ample explanations of the frequent editions that have appeared.

A Textbook of Histology. By HARVEY ERNEST JORDAN, A.M., PH.D., Professor of Histology and Embryology, University of Virginia. Pp. 738; 610 illustrations (many in color). Seventh Edition. New York: D. Appleton-Century Company, Inc., 1937. Price, $7.50.

Textual changes, not lengthy, chiefly concern the periosteum, ovaries, suprarenals, thymus and pineal. Thirty-nine illustrations have been replaced; it is to be hoped that many more of the antique figures will be replaced in future editions.

Diseases of the Heart. Described for Practitioners and Students. By SIR THOMAS LEWIS, C.B.E., F.R.S., M.D., D.Sc., LL.D., F.R.C.P., Physician in charge of Department of Clinical Research, University College Hospital, London; Honorary Consulting Physician to the Ministry of Pensions, etc. Pp. 297; 45 illustrations. New York: The Macmillan Company, 1937. Price, $3.50.

The virtues and defects noticed in the Review (*Am. J. Med. Sci.*, **186**, 439, 1933) of the first edition of this book are found unchanged in the present edition. According to the author, the text has been thoroughly revised "and all recent and relevant advances in our knowledge which it is judged will prove of value to practitioners, have been incorporated." Leaving aside the questionable punctuations, we doubt if this statement can be taken literally.

The Human Body. By LOGAN CLENDENING, M.D. Pp. 452; 106 illustrations by W. C. SHEPARD and DALE BERONIUS and from photographs. Third edition, corrected, enlarged and rewritten. New York: Alfred A. Knopf, Inc., 1937. Price, $3.75.

A Textbook of the Practice of Medicine. By Various Authors. Edited by FREDERICK W. PRICE, M.D., C.M., F.R.C.P., F.R.S. (EDIN.), Consulting Physician to the Royal Northern Hospital; Senior Physician to the National Hospital for Diseases of the Heart, London, etc. Pp. 2038; 112 illustrations. Fifth Edition. New York: Oxford University Press, 1937. Price, $12.50.

A Textbook of Medicine. By American Authors. Edited by RUSSELL L. CECIL, A.B., M.D., Sc.D., Professor of Clinical Medicine, Cornell University Medical College; Associate Attending Physician, New York Hospital, New York City. Associate Editor for Diseases of the Nervous System, FOSTER KENNEDY, M.D., F.R.S.E., Professor of Neurology, Cornell University Medical College; Director, Department of Neurology, Bellevue Hospital, New York City. Pp. 1614; 42 illustrations. Fourth Edition, revised and entirely reset. Philadelphia: W. B. Saunders Company, 1937. Price, $9.00.

PROGRESS
OF
MEDICAL SCIENCE

THERAPEUTICS

UNDER THE CHARGE OF

CARY EGGLESTON, M.D.,

ASSISTANT PROFESSOR OF CLINICAL MEDICINE, CORNELL UNIVERSITY MEDICAL COLLEGE, NEW YORK CITY,

AND

SOMA WEISS, M.D.,

ASSOCIATE PROFESSOR OF MEDICINE, HARVARD MEDICAL SCHOOL, BOSTON, MASS.

INSULIN.

THE number of publications during the past 5 years concerning insulin has been so large that it would be almost impossible to review all the material in print. Literally, thousands of papers dealing with insulin from one or another viewpoint have appeared, and it is obvious that some limitations had to be decided upon in a review of this type. We have chosen, therefore, to present the subject—insulin—from two viewpoints: (1) the increase in the therapeutic range of the hormone, and (2) the recent developments of various insulin retards.

The Use of Insulin in Non-diabetic Conditions. Even though insulin was originally intended as a chief remedial measure for diabetes mellitus, it has been used for almost every pathologic entity and ailment to which human flesh is heir. This increase in the therapeutic range of insulin in non-diabetic states is even more remarkable since there is no sound physiologic or pharmacologic basis for its use. Yet, on purely empiric grounds insulin has been used in the treatment of: 1, diseases of the lungs;[2a,b,8,64,71] 2, heart;[22,38,43,46,60,75] 3, kidneys;[10,53] 4, gastro-intestinal disorders;[21,24,34,36,67,77,86] 5, pernicious anemia;[11] 6, diseases of the joints;[15,19] 7, in cases of simple undernutrition;[13,31,56] 8, in obliterative vascular diseases;[10,19] 9, in menstrual disorders;[4,42,50] 10, in diseases of the skin;[80,87] 11, allergic states;[83a,b] 12, in drug addiction;[18,57,66] 13, in hepatic disorders;[12,16,51,82] 14, in various psychoses, chiefly schizophrenia;[27,66,74,79,87] 15, in neurologic conditions;[68] 16, to stimulate sexual development;[85] 17, in the study of experimental tumors;[45] 18, and even in the treatment of hyperinsulinism itself.[35] Such an extensive use of the hormone is most remarkable since excellent therapeutic results have been reported in *all* the pathologic entities treated. A careful study of these data reveals that many of the abnormalities treated often recover spontaneously and, therefore, the therapeutic usefulness of insulin in such instances is open to question.

Furthermore, many reports deal with a single case, or a small series of cases, and such reports are not very convincing. There are, however, non-diabetic states in which insulin has been used with results reported so startling as to warrant some detailed comment. The series of cases presented have been large, and the conditions reported as most benefited may be divided into three groups: 1, simple undernutrition; 2, pulmonary tuberculosis; 3, the psychoses—chiefly schizophrenias.

Insulin in Simple Undernutrition. It is now well established that insulin can be used to increase the weight of thin but otherwise healthy subjects. The therapeutic principle is based on the fact that mild hypoglycemia induces hunger, and stimulates the appetite, thus causing the individual to eat more. It is obvious that in any person, if all other factors are unaltered and the food consumption increased, that a gain in weight must result. The method usually employed was to administer 10 units of insulin about 3 times a day about ½ hour before meals. The diet was liberal. The individual injections were increased in number or dosage until a satisfactory result was obtained. All observers report gains in weight. Himwich and Nahum[31] gave their patients 3 units of insulin every 3 hours increasing gradually to 10 or more units. They treated 4 patients and reported such gains as 22½ lbs. in 23 days and 15 lbs. in 39 days. Metz,[56] using larger doses of 20 to 30 units 3 times a day, reported weight increases of 15 to 25 lbs. Blotner,[13a,b,c] who has probably had the greatest experience with this method of treatment, stated that the use of insulin to produce gain in weight in certain undernourished cases is "reasonable, uncomplicated and a practical method of treatment." In a series of 79 thin, healthy adults, Blotner reported an immediate and rapid gain in weight on 10 units 3 times daily. By tissue studies he demonstrated that the gain in weight was due not to water retention, but to actual deposit of fat.

It must be remembered that while unanimity of opinion exists, that an individual can be made fat as long as proper doses of insulin are given, not every one is in accord as to what happens to such persons once insulin is discontinued. This is an important consideration before recommending this form of treatment. Not all thin individuals can be "made fat" permanently. Some of them are thin by heredity. Their appetite is excellent and their caloric intake exceeds their calculated requirements. Their basal metabolic rate is within normal limits. Yet, in spite of all such normal factors and a liberal diet they fail to gain weight. It is certainly quite possible to make them gain by means of insulin. But, when insulin is discontinued, their weight gradually falls to its original level.

Insulin in Tuberculosis. Probably the largest series of cases of pulmonary tuberculosis treated with insulin was published by Allen, Douglas, Warren and Pottenger.[3] They treated 134 cases of all grades of severity, and whenever good therapeutic effects were demonstrable, the improvement was not in the tuberculosis but in the nutrition of the patient. Insulin proved of value in the cases of pulmonary tuberculosis in combating such symptoms as anorexia and serious malnutrition. A gain in weight as well as strength, an improvement in well-being and spirits were conspicuous advantages of the treatment. The authors admit that in the most severe cases insulin is useless; but as there are no contraindications, it may be worth while giving this form of therapy

a trial. Alien[2] and his associates state that insulin is of value not only because of its effect on appetite, but because it may alter defects in the metabolism of carbohydrate, which they found to be present in 40% of 128 patients with pulmonary tuberculosis. Abnormal glucose tolerance curves were found in these patients. Spellberg and Rosenblum,[76] using insulin in 13 cases of far-advanced pulmonary tuberculosis, stated that all of the patients showed improvement in appetite and gastric symptoms; 1 patient gained as much as 24 lbs. These authors did not claim that insulin was a specific cure for pulmonary tuberculosis, but it was their opinion that it helped by improving gastric motility, secretion and storage of glycogen in the liver and of fat subcutaneously. Banyai and Jurgens[8] studied the effect of insulin in 43 non-diabetic patients with active, moderately- and far-advanced pulmonary tuberculosis. Insulin was of value in that it improved the appetite in 19 (79%) of the 24 moderately-advanced cases and in 11 (57%) of the 19 far-advanced cases. The weight was increased in 54% of the moderately-advanced and 47% of the far-advanced cases. The above three reports are representative of the conclusions in connection with the use of insulin in non-diabetic pulmonary tuberculosis. It is apparent that its chief virtue lies in its ability to stimulate the appetite and increase the patient's weight. Insulin is not a "cure" for tuberculosis. The evidence that the use of insulin in tuberculosis is justifiable, because of a disturbance of carbohydrate metabolism, as evidenced by abnormal glucose tolerance curves is not convincing, as almost any infectious process as well as starvation will under certain conditions produce abnormal glucose tolerance curves. From the data given and from groups of smaller series of cases it is clear that whatever virtue insulin may have in the treatment of non-diabetic tuberculosis, it has no direct effect on the tuberculosis itself. Its great therapeutic value lies in its ability to stimulate the appetite thereby increasing the weight of the patient just as it does in cases of simple undernutrition.

Insulin in the Treatment of Schizophrenia. About 4 years ago, Sakel,[66b] of Vienna, reported a new method of treating psychoses, based upon the induction of hypoglycemic coma by means of large doses of insulin. His results, particularly for the treatment of schizophrenia, were so encouraging that numerous investigators have adopted it, and, as a result, in a short period of time there are available in the literature hundreds of case reports showing the benefits from the use of insulin in a condition that has always been regarded as practically hopeless.

The history leading up to the use of large, shock-producing doses of insulin is interesting. Insulin was first used by many[27a,b,c,66a,b,74,79,87b,c,d] in cases of mental diseases as a means of improving appetite and nutrition. But, in the course of such therapy, Strecker[79] noted improvement among some disturbed patients after an unexpected insulin reaction. Mebel[87] and, at about the same time, Jacob and Doussinet[87] reported cures in psychotic patients to whom large doses of insulin were given. Other favorable results were being published from various clinics, but the specificity of insulin as the effective agent was not particularly emphasized, until Sakel presented his results. This investigator was the first to advocate the use of shock-producing doses of insulin for the treatment of schizophrenia. Following his reports abroad, Glueck,[27a,b,c] Wortis[87b,c,d] and others in this country have treated schizophrenic

patients with insulin and they have publicly stated that the method has promise. Sakel has personally treated over 300 cases, and, although the evaluation of the results is difficult because of spontaneous remissions which occur in schizophrenia, yet in the first 100 cases he has had 88% "good or full remissions." These patients could resume their work. Since spontaneous remissions occur in only 5 to 20% of the cases, it is obvious that treatment with insulin offers considerable hope. Sakel induced hypoglycemic coma by varying doses of insulin. He stated that the management of the coma so induced is much more important than its production, as the therapeutic results depend upon the proper termination of the hypoglycemic coma. As yet, he has not evolved any criteria by which one can judge when the hypoglycemia should be terminated. This was usually done by administering glucose by stomach tube or intravenously. Occasionally, though rarely, adrenalin had to be given. To quote Sakel:[66b,c] "When the treatment first developed I could not say exactly why I terminated the hypoglycemia at one point in one case and at a different point in another case, or why I should vary the period of hypoglycemia in the same case in different stages of treatment. The probability was that I was guided by dim unconscious recollections of previous experiences in similar cases." Sakel at first was of the opinion that only the early cases should be treated, but after his experience with over 300 cases he felt that some chronic cases may also benefit from this type of treatment. Glueck,[27a,b,c] who has had experience with this method, also remarks that the technique cannot be readily standardized. Wortis,[87b,c,d] reporting on 13 cases, stated that 9 have "definitely benefited from the treatment and 4 have so far been unresponsive." He recorded the interesting observation that a hypoglycemic reaction will usually follow a similar pattern every time a hypoglycemic state is induced. This fact has been observed among diabetic patients in whom successive reactions occurred because of excessive doses of insulin.

Smith[74] felt that, in view of the beneficial results reported in the treatment of the psychoses, insulin therapy might be applicable to "at least some neuroses," and after treating 8 cases he stated that "insulin therapy proved effectual in treating both psychotic and psychoneurotic patients."

Because of such dramatic reports, dealing with hundreds of cases, it is not difficult to understand the enthusiastic and hopeful reception this method of therapy has to date enjoyed. It has been widely publicized in the lay and medical press. There is no doubt that it merits much consideration, as there is no medical treatment for schizophrenia and psychotherapy has not been encouraging. Yet, there still remains a large group of conservative physicians who advise extreme caution before accepting insulin as a specific for schizophrenia.[20] It is to be emphasized that there is nothing specific either pharmacologically or physiologically to support the use of insulin in the treatment of the psychoses. Perhaps the published results justify such a procedure on an empiric basis, because it offers some tangible method of therapy for a condition for which no other treatment is known. Yet, if accepted, it must be employed with considerable caution until its mechanism is understood and a relatively standardized, rather than an intuitive technique, for its application is developed.

Insulin "Retards."* If it is assumed that diabetes mellitus is due to a defect in the insulin producing mechanism, then the artificial administration of this hormone should in a way compensate for such a deficiency. As a matter of fact it does. This dictum, therefore, may be stated without reservation—*Insulin benefits all patients presenting a group of symptoms or syndrome known as diabetes mellitus.* That it is only a substitution therapy is also well established. Some cases of diabetes need a smaller and others a larger amount of insulin to restore the metabolism of carbohydrate, at least approximately to a physiologic state. Since insulin is effective only when given parenterally, it is obvious that in the severe cases either *more* insulin will have to be given at one time or more frequent doses throughout the day. Both experimental and clinical experience have demonstrated that frequent small doses are much more effective as aids in the utilization and storage of carbohydrate, than the same quantity given at one time. In practice, therefore, it is the routine to administer 3 or 4 injections of insulin to the severe diabetic. Three are given 20 to 45 minutes before meals and the fourth either at bedtime or during the night. The criteria of satisfactory therapy, from the laboratory viewpoint, have been a sugar-free urine and a blood sugar curve approximating the normal configuration. Such desiderata were not always attainable as there were patients whose blood sugar would fluctuate from the hyperglycemic to the hypoglycemic level with the result that the patient would be on the verge of ketosis at one time and insulin shock, or even hypoglycemic coma at another. It was felt that these profound fluctuations were due to the rapidity of action of the administered insulin. The obvious approach to this problem, therefore, was to *slow up or retard* the action of insulin. If insulin could be so altered as to render its action slower, then the precipitous fall of the blood sugar and presumably its disagreeable symptoms, could be avoided. Since most investigators were of the opinion that the rapidity of action was due principally to the fact that insulin was rapidly absorbed, methods were sought to slow down its absorption. That is the cardinal principle of all slow acting insulin preparations.

A. Lipoids. There have been attempts to retard the action of insulin by mixing it with oils, cholesterol, lecithin, or combinations of the three. Leyton[49] used lecithin and various oils and felt that the insulin was more slowly absorbed when mixed with oil. Skouge and Schrumpf[72] presented evidence based on animal experiments and normal men that lecithin acted as a retard. They found that the blood sugar fell more slowly with the insulin-lecithin compound. Recently, Katsch, Scholderer, and Klatt[41] have compounded a viscid insulin preparation which they have called "insulin durant." The character of the base used was not fully described, but from some of its properties it may be assumed to be lipoid. They have used this product in 23 cases, and they were able to get along with *one* injection every 2 or 3 days instead of 3 injections daily. The material is injected intramuscularly and because of its marked viscidity it is put up into carpules which have rubber caps at both ends. The carpule is then placed into a metal syringe,

* Retard is a substance which slows the pharmacologic action of the product with which it has been mixed.

from which the injection is made. With this compound they gave as much as 330 units of insulin at one time.

In general, the use of oils as retards has not been adopted. The results were not sharp and an additional drawback was the local reaction—pain and swelling. The "insulin durant" may be of greater practical application, but as yet the data are insufficient from which to draw definite conclusions.

B. Vasoconstrictors. The thought then occurred to some that since it is not practical to bring about a delayed absorption of insulin by physical means such as an oil suspension, that it might be done by decreasing the blood supply of the area into which insulin was to be injected. It has been known from the time of the discovery of insulin that this hormone and pituitrin were antagonistic. That is, if insulin and pituitrin were given at the same time, the insulin did not exhibit its blood sugar lowering effect. This reaction Wermer and Monguio[84] think is due to the vasoconstriction produced by the pituitrin, and because of this fact, insulin can enter the circulation very slowly. Claussen[44b] was able to slow down the absorption of insulin by adding to it small quantities of adrenalin or pituitrin. There were no unpleasant reactions from the vasoconstricting drugs used. Anderson,[6] employing Claussen's technique, treated 17 cases of diabetes. The procedure was to add 0.1 mg. of adrenalin to 5 cc. of insulin and use the necessary dosage as each patient's condition demanded. It was observed that this mixture did not produce symptoms of hypoglycemia, whereas a like quantity of insulin alone did. The decrease in the blood sugar lowering rate was attributed to the slower absorption of the insulin containing the vasoconstrictor.

C. The Salts of Heavy Metals. In 1934, Maxwell[54] observed that the addition of zinc salts to hypophyseal gonadotropic extracts increased their potency. He stated that the action of zinc consisted in retarding the absorption of the active principle. It has also been shown that zinc prolonged the activity of insulin.[68a] Furthermore, Maxwell and Bischoff[55] found that not only zinc, but other metals possess a similar action. They added basic ferric chloride to insulin and found that its absorption from the parenteral depots slowed down. Fazekas and Himwich[23] were able to demonstrate this prolonged action with salts of aluminum. Cobalt and nickel have also been used to delay the absorption of insulin. It is, therefore, apparent that when the salts of a variety of heavy metals are added to insulin, a change occurs which prolongs the activity of insulin, without affecting its pharmacologic properties.

D. Tannic Acid and Safranin O. Maxwell and Bischoff[56] found that the addition of tannic acid to insulin would also result in a slow acting product. A compound made of 4 mg. of tannic acid and 5 cc. of insulin was shown by Gray[28] to act more slowly than the unmodified insulin. However, the insulin-tannic acid compound caused local reactions such as painful swelling and redness.

Another slow acting insulin preparation was introduced by Jacobs and Ricketts.[33] They mixed equal parts of a 0.5% aqueous solution of safranin O and insulin of the U 40 concentration. They then adjusted the pH to the weakly alkaline side (7.2) and obtained a precipitate

which, when injected into animals, caused a hypoglycemia of gradual onset and extended duration.

E. Histone-Insulin. This preparation was proposed by Gray, Bischoff and Sansum.[29] They combined histone, a simple protein, with aqueous insulin. Disodium phosphate was then added and the pH adjusted to 6.7, at which point a finely divided precipitate was formed. The histone-insulin thus formed was used in the treatment of 30 diabetic patients. They reported that it was capable of controlling human diabetes when used alone, that its action was slower than aqueous insulin and that no local or systemic reactions were observed.

It may be of interest at this point to inquire why the addition of heavy metals, histone, tannic acid, or safranin O to insulin results in a compound whose action is of longer duration. The explanation for this phenomenon is lacking. It has been assumed that in the case of the heavy metals this prolonged activity could be explained on the basis of catalysis. This hypothesis cannot be applicable to the tannic acid or the safranin O compound. It seems to us that the following hypothesis might be suggested. As the salts of heavy metals and tannic acid are protein precipitants, it is not at all unlikely that proteins in the subcutaneous areas are precipitated by them, when such metals or tannic acid are injected subcutaneously. As the coagulum or perhaps many coagula are formed, insulin is bound up within them. In time these particles are acted upon by the tissue juices and the insulin gradually liberated, thus prolonging its action.

Sahyun[65] prepared a crystalline insulin which is completely soluble at pH 6.4 to 7.0. When a solution of this preparation was made it was found that its action was considerably prolonged. Barach[9] used crystalline insulin in the treatment of 21 cases of diabetes mellitus and concluded that this preparation lowered the blood sugar to a greater extent and for a longer time. He also observed that insulin reactions occurred less frequently than when commercial insulin was used. With the exception of some minor differences of opinion, all investigators[25,52,61] who have had experience with crystalline insulin agree that its action is prolonged. Altschuler and Leiser[5] stated that the pharmacologic effect of crystalline insulin may last as long as 14 hours, and because of this prolonged action permit better control of the diabetic patient. Most of the investigators suggested that the prolongation of its activity was due to its zinc content. There may be a qualitative relationship, but certainly no such quantitative factor could be demonstrated. Barach[9] felt that the greater alkalinity of this product when in solution was the factor responsible for its slower action. He stated that "The greater the alkalinity the slower the absorption of insulin." From the published evidence it is obvious that crystalline insulin acts more slowly than regular insulin, but the explanation for this phenomenon will have to await future developments.

Protamine Insulin. Most of the above methods of slowing up the activity of insulin were interesting but not practical. They could not be used in the treatment of diabetic patients. To Hagedorn,[30] however, credit is due for the discovery of a substance which retards the activity of insulin and which at the same time is of tremendous practical value. The substance used was protamine—a simple protein. This was mixed with insulin, and the resulting product was called protamine insulinate.

When this product became available it was supplied in two vials—protamine in one and insulin in another. The protamine was so buffered that when the two were mixed the pH changed from 3.5 to 7.2, that is, to the alkaline side. The mixture had a milky appearance due to the suspension of fine flocculent particles. On standing, protamine insulinate would separate into two layers—a white flaky one and a clear, colorless, supernatant fluid. Before using, it had to be shaken gently to make the distribution of the particles uniform, and, like insulin, it had to be used parenterally. Krarup,[44a] after using this preparation for $2\frac{1}{2}$ years, reported no deleterious results. No undesirable local or systemic reactions were noted by him in the treatment of 41 diabetic patients. He demonstrated in a convincing fashion that protamine insulinate lowers the blood sugar more slowly than insulin and that its action is prolonged. Here, then, was a preparation which was free from deleterious effects, local or systemic, which had practical possibilities, which lowered the blood sugar slowly, thus eliminating sharp sudden hypoglycemic states, and which because of these properties suggested a very desirable improvement in diabetic therapy, namely: the diminution in the number of daily injections.

When this product was first announced, certain pharmaceutical firms placed the material at the disposal of a large and representative group of physicians. Protamine insulinate, or protamine insulin, as it was being called, was thus subjected to much clinical trial. In a short period of time a voluminous literature accumulated and most of the workers commented very favorably. Clinicians[1,14,26,32,40,47a,48,59,62,63,70,73,78] agreed that the new insulin acted more slowly and that its action was prolonged. The reason for this property is that it is relatively insoluble in the subcutaneous tissues and is therefore more slowly absorbed than the aqueous acid regular insulin. The protamine and the aqueous insulin when mixed produce a physico-chemical reaction in which adsorption plays a dominant rôle. Each flocculent particle adsorbs a certain amount of insulin as if it were a small particle of charcoal. When these congregate particles are administered parenterally, they are acted upon by the tissue juices, and as they are broken down the insulin is liberated and absorbed. The action of protamine insulin, therefore, should be directly proportional to the time required by the tissue juices to liquefy the precipitate. This, however, is unpredictable on theoretical grounds and certainly clinically one can only approximate the duration of the active phase of the product. Its duration of action has been given as from 12 to 24 hours. Regular insulin on the other hand is absorbed rapidly and its pharmalogic effect lasts from 4 to 6 hours.

It is now well recognized that the moderately severe and severe diabetic patient has a rising blood sugar during the night even if no food is taken. Hagedorn[30] and his associates felt that protamine insulin given to these patients would counteract the nocturnal blood sugar elevation, and he has also found it possible to obtain a normal fasting morning blood sugar by giving an adequate amount of the new insulin in the evening. His technique was to give soluble insulin in the morning to reduce the elevation of the blood sugar which resulted from the digested carbohydrate, and the insoluble insulin in the evening to maintain the blood sugar at approximate normal levels. This was a most logical beginning, and it was based on sound physiologic principles.

It is not unreasonable to assume that the production of insulin in the organism is subject to variations depending on requirements. This is a cardinal principle in physiology. If one is quiet, the metabolic processes are at a lower ebb than if one is very active. Less gastric juice is secreted during fasting than during a good meal. And so with the production of insulin, a carbohydrate-rich meal is provocative of greater quantities of insulin than a meal of fat or fasting. It is also probably true that the secretion of insulin goes on continuously; otherwise, even in the normal individual the blood sugar would be subject to great variations at night. It is on such a hypothesis that Hagedorn formulated his technique for the use of protamine insulin. The method, while not decreasing the number of injections in all cases, maintained the blood sugar curve throughout the 24-hour period at a level approximating normality.

At this point many clinicians began to use protamine insulin, and modifications of the original technique have resulted from their collective experience. However, no standard technique is as yet available. Most investigators felt that advantage of the prolonged action should be taken and thereby attempt the control of the diabetes by means of a single large dose. Wilder[65] stated that the action of a single dose might extend into the third day and that its immediate effect was slight. He administered protamine insulin in a single large dose in the morning, at times with, and at times without, regular insulin. He noted that when protamine insulin was used alone in a large single dose, a postprandial glycosuria occurred at first; but that the "end of the fourth to the sixth day a normal level of blood sugar may be obtained even in severe cases." Sprague and his associates[78] also treated diabetic patients with one injection of protamine insulin, giving the entire daily dose before breakfast. This procedure was followed by others and, though usually satisfactory, in severe cases had to be supplemented by regular insulin to prevent the postprandial glycosuria. Lawrence and Archer[47] found a single dose of protamine insulin satisfactory with mild cases, but in the severe cases large single doses of 60 to 100 units would not prevent a glycosuria. Campbell, Fletcher and Kerr,[17] on the other hand, found that a single dose of 50 to 60 units of protamine insulin will bring about "fair" control in most severe cases requiring 60 to 100 units of insulin, given in 3 or 4 injections. These investigators were careful to state, however, that in some cases 2 injections of protamine insulin may be more effective in controlling a glycosuria. Joslin's[39e] counsel in connection with the use of protamine insulin is very sound. He stated that one must be patient, as good results may not show "for several days, a week or longer." He also advised that one change very slowly from the regular to the protamine insulin, allowing a week for the transfer. It was his policy, at first, to hospitalize the patients who wished to transfer from the old to the new insulin.

As the results of the treatment of diabetes with protamine insulin began to appear, all agreed in one respect, that the blood sugar was lowered gradually and that the action of the product was prolonged. Most were of the opinion that the diabetes improved considerably. The use of fewer injections gave patients more freedom, which was of psychologic value. The patient claimed that he definitely felt better. All of this was true, but it was equally true that it was practically impossible in some cases of diabetes to maintain a urine free from sugar.

Some of our patients receiving protamine insulin gained weight, felt well and were free from symptoms, but a marked glycosuria was present throughout the greater part of the day. An analysis of these divergent opinions revealed that two important variables were at work: 1, diet and, 2, technical differences in the administration of the protamine insulin.

Diet. Hagedorn used high-fat diets with about 100 gm. carbohydrates. Campbell, Fletcher and Kerr[17a] used also diets high in fat and low in carbohydrate. Joslin's diets were more generous in their carbohydrate content. Rabinowitch, Fowler and Corcoran,[61] on the other hand, employed the high carbohydrate-low calorie diet. They were able to control their cases with a single daily dose of protamine insulin. Using similar diets we were not very successful in maintaining our patients free from sugar on one dose of protamine insulin alone. Campbell and his associates[17b] felt that more satisfactory regulation of the diabetes with protamine insulin could be affected with diets *low in carbohydrate*, and furthermore that it was more feasible to maintain the urines of such patients free from sugar by one daily injection.

Technique. As diabetic patients vary, it is obvious that almost individual methods had to be evolved for each patient. As a result the following combinations of protamine insulin with or without regular insulin have been used.

a, Regular insulin in the morning, protamine insulin in the evening; *b*, protamine insulin in the morning, regular insulin in the evening; *c*, protamine insulin and regular insulin in the morning—these were to be given in separate syringes and into different sites; *d*, large, single, daily doses of protamine insulin in the morning; *e*, protamine insulin and regular insulin in the morning *and* in the evening.

From the data published it appeared that protamine insulin had great possibilities. Of the disadvantages mentioned the chief ones were that: *a*, the protamine and insulin had to be mixed aseptically by the physician or patient; *b*, that the mixture was not very stable and at first it was even recommended that it be discarded after a week's time; and, *c*, that the reactions due to overdosage were somewhat different from those of regular insulin. Fortunately, the question of stability of the mixture required little attention as at this time a supposedly more stable compound was introduced. It is to be stated, however, that Rabinowitch[61] and his associates demonstrated that protamine insulin may show no deterioration after 135 days. Lawrence[47a] also felt that it was more stable than generally believed.

Protamine Zinc Insulin. Scott and Fisher[68b] showed that the addition of small quantities of zinc to protamine insulin produced a *more stable* and *longer acting compound*. Furthermore, the addition of the zinc obviated the necessity of two separate vials for mixing. It could be supplied already mixed. The mixture has a milky appearance, it is stable, it is obtainable in two concentrations, 40 and 80 units per cc., and it contains 0.2 mg. zinc per 100 units. Protamine zinc insulin has replaced the older preparation of protamine insulin.

From the data of the experiences recorded in connection with the use of protamine zinc insulin, clinically and experimentally, the following conclusion may be drawn:

1. It retains its potency for several months after mixing.
2. During the first 3 to 6 hours it shows little if any effect on the blood sugar.
3. Its slow action is due entirely to the slow rate of absorption from the parenteral depots.
4. It lowers the blood sugar slowly.
5. Its pharmacologic effect continues for at least 24 hours when used in moderate doses, and longer with larger ones.
6. That in cases of moderately severe and severe diabetes it must be supplemented with the soluble or regular insulin to eliminate the postprandial hyperglycemia and glycosuria, particularly if a liberal carbohydrate diet is used.

The technique for its application is still varied. Some clinicians select a definite unitage as a starting point, and after 2 or 3 days alter the dose, being guided by the glycosuria and the blood sugar level. Lawrence and Archer[47b] begin with a basal dose of 30 units. They then examine two specimens of urine—one immediately on awakening; the other before breakfast. The first specimen represents the urine voided soon after bedtime; the second the urine secreted before breakfast, this being the more informative one. If the second specimen is sugar-free it is an indication that the dose of protamine zinc insulin has been sufficient—providing there are no symptoms of overdosage. If the second specimen contains sugar then the quantity of the preparation must be increased. This simple and most informative procedure will suffice in the mild or even moderately severe cases. In the severe type of case regular insulin will have to be added to take care of the immediate carbohydrate load. Lawrence and Archer[47b] state that both the protamine zinc insulin and soluble insulin can be mixed in one syringe and injected into one site. They claim that such mixing does not interfere with the individual properties of each preparation.

Another method of arriving at the required dosage is to give about 75% of the total daily dose of insulin as protamine zinc insulin, supplementing it with regular insulin and adjusting the amount up or down according to the urine and blood tests. Whatever method is employed it is obvious that each patient is an individual problem and must be carefully studied before satisfactory adjustment can be made. Joslin[39b] is of the opinion that protamine zinc insulin is an advance in the therapy of diabetes and from his experience with 1250 cases he is extremely enthusiastic over the results.

Reactions. The subject of the frequency and type of reactions resulting from the use of protamine zinc insulin has not been sufficiently discussed.

From the first experiences it was the belief that the reactions were mild and infrequent. Then gradually warnings regarding the subtleness of the reactions began to appear, Allen[2b] being among the first to observe this. Wilder[65] stated that he heard of 1 death resulting from protamine zinc insulin, and he believes that the reactions have been "unduly minimized." Lawrence and Archer[47b] also mention the hazard of reactions because of the lack of prodromes, such as sweats, trembling and shakiness. Jordan[37] found unconsciousness in 6 out of 17 cases from protamine zinc insulin. While he attributes some of this to carelessness in carrying out the advised treatment, yet hypoglycemic reactions were

also troublesome in the patients who followed instructions and were receiving only 1 daily injection of protamine insulin alone. Tolstoi[81] has reported his experiences with reactions. Severe reactions occurred in 5 out of 15 patients. All patients were experienced diabetics and were fully familiar with the premonitory symptoms of hypoglycemia. Yet, some were not aware that anything was wrong until they became unconscious and had to be revived by means of intravenous glucose or adrenalin. In 4 of the cases reactions took place 24 hours after the injection even though the patients were receiving liberal carbohydrate diet. In no instance were the doses over 45 units at one time. The explanation for the subtleness of reaction and its suddenness is probably that the blood sugar is lowered so gradually that tremor, sweats, shakiness and palpitation are absent. Tolstoi has also stated that the reactions due to protamine insulin may strike suddenly, without warning, and once established may last a long time.

Summary. The above review has presented the extradiabetic uses of insulin, of which there are many. The application of this hormone in some pathologic conditions has been based on physiologic principles; in others on purely empiric grounds. Even though miraculous results have been reported, it is difficult to ascribe the therapeutic benefits to insulin alone. One cannot deny, however, that insulin stimulates the appetite and can be of value in disease or health when it is desirable to increase the body weight. Insulin, as a cure for schizophrenia, has had considerable publicity and hundreds of cures can be found in the literature. In spite of the enthusiastic reports, experienced psychiatrists, while keenly interested advise great caution and patience.

We have also presented the arguments for the need of a slow acting insulin and described most of the preparations used. An attempt has been made to explain the *modus operandi* of each. It will be seen that to date the most practical slow acting insulin is protamine insulin to which zinc has been added. The technique employed in connection with its clinical application have been described and the symptoms as well as the hazards resulting from overdosage have been presented.

EDWARD TOLSTOI, M.D.

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RADIOLOGY

UNDER THE CHARGE OF
ALBERT MILLER, M.D.
AND
CHARLES G. SUTHERLAND, M.D.
CONSULTING PHYSICIANS SECTION ON ROENTGENOLOGY, MAYO CLINIC, ROCHESTER, MINN.

LOW BACK PAIN.

Low back pain associated with so-called sciatic radiation has been recognized for centuries as a clinical entity. The obvious localization of pain in the low back frequently associated with a deformity of the spine early led to the conclusion that the radiation of pain in the leg was produced by some lesion in the low back. Various explanations, such as myositis, joint infection, lumbosacral abnormalities or derangement of the sacroiliac joints, have each in their time held sway as the plausible etiologic factor for this symptom-complex of sciatic irritation associated with low back pain. Interest has been stimulated by the possibilities of mechanical nerve irritation demonstrated anatomically by Danforth and Wilson,[7] and substantiated clinically by Putti,[23] Ayers[1] and later Williams.[25] With this introduction Badgley[2] presented the clinical features of low back pain with sciatic radiation observed in a study of 447 cases as a prelude to the roentgenographic study reported by Hodges and Peck.[11] The clinical picture of this group was characterized by the onset, sudden or gradual, in an hitherto normal individual, of low back pain associated with a radiation of pain into the lower extremity along an almost constant pathway in the posterolateral part of the extremity, the buttock, the anterolateral and posterolateral part of the thigh and the anterolateral part of the leg and foot. The cases were subdivided into three groups, all with low back pain and radiation into the lower extremity, but differing in the extent of radiation or deformity: 1, Typical sciatic scoliosis characterized by the symptoms of low back pain with radiation usually along the described pathway in the lower extremity plus the development of a list of the trunk away from, or toward the affected side, rarely the list alternating to one or the other side. 2, Symptoms of low back pain, with radiation the full extent of the lower extremity without the list, or a history of the list. 3, Low back pain with radiation of pain into one or both buttocks, associated with pain deep in the thigh. No pathological process that precluded the possibility of spontaneous return to normal function was included in this study, thus ruling out all cases of tuberculosis, tumors, osteomyelitis, and so forth.

The more characteristic symptoms were briefly: 1, Pain, seeming to center about the posterior sacroiliac region into the buttock, deep in the thigh in the posterolateral portion, following the peroneal division of the sciatic nerve. This pain was generally constant, aggravated by motion or change of position. The radiation pain was also usually constant, but occasionally intermittent and brief in nature, brought on

by sudden unguarded movement. No case presented radiation of pain along the tibial nerve distribution and only a small number had radiation of pain on the mesial side of the thigh. 2, Guarded motion of the spine was early assumed by the patient. Spinal motion was prevented as much as possible by unusual use of the arms in changing positions such as getting up from a chair, or turning over in bed. 3, A list of the trunk was present in 173 cases (39%), away from the affected leg in 125 and toward the painful side in 81. In 233 cases (61%) the list was not present but there was a protective attitude on standing with the weight borne on the well leg, and the painful leg held in flexion and abduction bearing little weight. Commonly, the most comfortable attitude assumed by this group was to stand bent over the back of a chair or table with the weight borne on the hands, the affected leg flexed and abducted.

Clinical tests of definite value in the diagnosis were: 1, Straight leg raising was usually limited, generally more limited on the painful side, frequently producing pain in the low back in the lumbosacral or sacroiliac region. This was probably due to the contraction of the lumbopelvic muscles, altering the tilt of the pelvis and producing an apparent shortening of the hamstring muscles. 2, Patrick's sign, forced abduction of the flexed thigh producing pain in the sacroiliac region, was not commonly present. Compression of the iliac crests rarely elicited pain. Where these tests were positive they tended to incriminate the sacroiliac joint as the seat of the lesion. 3, Nachlas' sign, hyperextension of the thigh with the patient prone and the knee flexed, frequently produced pain in the lumbosacral region and was a test of the lumbosacral joint. 4, The prone thrust test, the patient lying prone, raising himself on his hands with elbows extended, and dropping the pelvis toward the table as far as possible, was used frequently. This produced hyperextension of the spine and in itself was frequently painful or impossible to carry out because of pain in the lumbosacral region. If not painful in itself, with the patient relaxed in this attitude, a sudden thrust over the lower lumbar spine sharply increased hyperextension and frequently produced severe pain analogous to the patient's symptoms. 5, Ober's sign, an attempt to adduct the extended abducted leg with the knee at right angles, the patient lying on the side, was infrequently used. The test was positive if the knee could not be brought to the table but remained in an abducted position and this was indicative of contraction of the iliotibial band. In cases with positive tests a high division of the iliotibial band (Ober's operation) has resulted in marked relief of symptoms. 6, Sensory changes were present in only 20% of cases, mild hyperesthesia or hypesthesia over the peroneal distribution. 7, The sites of tenderness in the 447 cases were tabulated as lumbar spine (63), lumbosacral (260), posterior iliac spines (212), lumbosacral articular facets (33), sciatic notch (195), deep nerve (66) and no point of tenderness (53). 8, Motor changes were exceedingly rare; there was muscular weakness probably due to disuse noted in 12 cases and a true paralysis in only 2 cases in the entire series. 9, The Achilles reflex was definitely altered in 80 cases (18%), usually diminution and less frequently complete absence. 10, Atrophy of $\frac{1}{2}$ inch or more of

the affected leg was frequently noted, this feature was practically constant in the severe chronic cases, undoubtedly on a disuse basis.

Males constituted 56.7% in this series. The average age, varying from 13 to 80 years, was 49.7 years. A few cases with prolonged symptoms of years' duration added somewhat to the average duration of symptoms of 4.24 years. Occupation seemed to play a definite part in the etiology; 168 were housewives, 91 unskilled laborers, and 84 skilled laborers. Trauma was regarded as a definite cause in only 25% of cases; 86 patients had sudden onset of symptoms immediately after trauma and 29 had a gradual onset which they attributed to a preceding injury. Without a history of trauma, 42 patients had sudden onset and 288 had a gradual onset of symptoms. There was but a single attack in 15 cases, recurrent attacks occurred with intervals of complete freedom in 230 cases, symptoms were constant in 108 cases and in 92 cases there were constant symptoms plus acute exacerbations associated with radiation of pain to the leg. The symptoms were recorded as mild in 183 cases, there was temporary incapacitation by the severity of the symptoms in 165 cases. Eighty-four patients were incapacitated from their usual occupation and 15 were completely incapacitated by the severity of the symptoms.

There was a characteristic pathway for radiation of pain arising from the region of the posterior spines of the ilium, over the buttock and trochanter, down the posterolateral and anterolateral surface of the thigh, the anterolateral surface of the leg and foot. The distribution of pain was not the distribution of the sciatic nerve. The area of involvement is the so-called dorsal axial surface of the leg which is supplied by the postaxial nerves of the anterior divisions which compose the lumbosacral plexus, and could be more properly called postaxial plexalgia.

Lumbosacral tenderness is not an uncommon finding in patients with just a low back pain, whereas the tenderness about the sacroiliac region was seen chiefly in this syndrome. Tenderness over the sciatic exit was also a frequent finding in this series.

The symptomatology was characteristically the same whether the roentgenogram showed a normal spine, congenital malformation, narrowing of the lumbosacral joint space, arthritis, or asymmetrical development. The type of skeletal change observed in the roentgenogram had no definite relation to the extent and location of the radiation of pain. It seemed plausible that a true neuritis was more apt to occur in the presence of definite lumbosacral lesions. The sensory changes also occurred with greater frequency in the abnormal Roentgen group than in the normal.

Hodges and Peck[11] made a routine Roentgen study of the dorsal, lumbar and sacral spine in all the cases clinically considered by Badgley and for purposes of comparison reviewed comparable spine films of a control group of cases. The findings of the two groups were tabulated. Narrow lumbosacral joint was noted in patients with low back pain and sciatic radiation in an approximate ratio of 4.5 to 1 found in patients with low back pain and no sciatic radiation. Lumbosacral anomalies were seen in approximately 2 patients with low back pain

and sciatic radiation to 1 with low back pain and no sciatic radiation. There was no significant difference in the study group and in the control group as regards osteoarthritic changes. The distribution of the different types of lumbosacral anomaly observed in the group of patients with low back pain and sciatic radiation was tabulated.

In his Hunterian lectures, Keith[13] described the human spine as a mechanism of the utmost complexity. Between the sacrum and the skull are incorporated 24 vertebræ, each provided with 3 short levers—the transverse processes and the spinous process. Each lever is furnished with not a single muscle, but a group of them. Passing from the sacrum to the skull one finds the levers change in length, strength, shape and direction. The muscles too which move and balance the levers alter in disposition and strength from vertebra to vertebra. The 12 dorsal vertebræ, besides their 3 short processes, are provided with very long and powerful levers—the ribs. They are the most powerful of the spinal levers. All the muscles attached to the ribs—the intercostals, the rectus abdominis, and the oblique muscles of the belly wall—are prime movers and balancers of the spine.

With the evolution of the upright or orthograde spine there took place a shortening of the lumbar part of the spinal column. The 3 vertebræ which became modified in the course of development to form the sacrum were the twenty-seventh, the twenty-eighth and the twenty-ninth. The twenty-seventh formed the first of the sacral series in the earliest mammals. In some monkeys the twenty-seventh showed some admixture of lumbar traits. In others, the twenty-sixth showed signs of forsaking some of its lumbar traits and adapting the characters of the first sacral. There was a tendency in some for the process of sacralization to spread in a tailward direction, in others the tendency was in a headward direction. In a majority of chimpanzees the twenty-fifth became the first sacral, but among the orangs the twenty-fourth (fifth lumbar) formed the first of the sacral series. In man, as in the chimpanzee and gorilla, the twenty-fifth formed the first of the sacral series. In a series of 100 human skeletons approximately 3 or 4 show a headward sacralization, while 6 or 8 show a tailward movement. In a similar number the eighteenth vertebra will bear the last rib in about 2, the nineteenth in 90 and the twentieth in 8.

The brunt of the evolutionary or adaptional changes fell on the spinal musculature of the lumbar region. The spinal musculature obtained an ever-increasing attachment to the sacrum and pelvis. The pelvis became more and more a fixed base from which the erector spinæ might act. In man the area for muscular origin was also increased by the backward tilting of the sacrum, so that its dorsal surface in the erect position looked upward as well as backward. The spine, transmitting the weight of the suprapelvic part of the body became poised on the anterior or basal end of the sacrum. The weight tended to tilt up the hinder or coccygeal end of the sacrum and would have done so were it not for, 1, the form and strength of the sacroiliac joints and, 2, because the hinder end of the sacrum was bound to the ischial tuberosities by those particularly strong stays, the sacroiliac ligaments. There was also a tendency, when the sacrum was set obliquely, for the basal end of the spine to be dislocated forward into the pelvis, giving

rise to the condition known as spondylolisthesis. Such a dislocation was prevented by the articular processes of the last lumbar vertebra being locked within those of the sacrum. A sudden jump, or a severe effort to lift or carry a heavy weight, might cause the laminar arch of the last lumbar vertebra to snap and thus permit a forward displacement of the spine. Keith found no evidence which would lead him to suppose that the separation of the arch of the last lumbar vertebra was the result of maldevelopment.

Kark[12] considered faulty posture to be the underlying cause of much genital change in women. The lumbar vertebræ are held in position mainly by the anterior and posterior common ligaments, the supraspinous and interspinous ligaments. These are kept taut or relaxed according to the attitude of the spine and are subject to strain. When this strain is constantly repeated or prolonged, aching results. The ligaments are reinforced by the sacrospinalis muscle, which extends from the sacrum to the cervical region. This muscle is a large muscular and tendinous mass, larger in the lumbar region than elsewhere, and it is by its aid that spinal movements take place and the trunk is held erect, the brunt of such action falling on the lumbosacral region. When this muscle is strained, therefore, or when it is not strong enough to carry out its normal or increased functions, aching results in the lumbosacral region. The frequent association of backache with such conditions as retroversion, subinvolution, dysmenorrhea, congestion of the pelvic organs, is probably due to the existence of a common etiological factor, namely, a weak back, loss of muscle tone and faulty posture. This might serve to explain why the treatment of retroversion and other gynecological disorders seldom relieves backache unless the back itself is treated, even to the neglect of a local displacement. The lumbar arch is in many respects analogous to the plantar arch in the foot. In the condition of flat foot, aching is caused by strain on the ligamentous structures of the flattened and weakened arch. This ache can usually be relieved by mechanically supporting the sagging arch. Further, by means of suitable exercises and massage, the muscles that normally support the arch are gradually strengthened until such time as the mechanical support can be dispensed with and the arch maintained by muscles and ligaments that have been rested and restored to function.

Goldthwait *et al.*,[10] in discussing the relation of body mechanics to disease, pointed out that the weight of the trunk and head rests mostly on the bodies of the vertebræ and the intervertebral discs. The articular facets normally act only as stabilizers. The articular processes of the adjoining lumbar vertebræ, with their facets, form the posterior wall of the intervertebral foramina. Where these two articular processes come together, there is a true joint with a capsule and ligaments. This joint has a normal range of motion. The amount of motion will vary with the shape of the facets. In the lordotic position of the lumbar spine the weight of the body is thrown backward upon the articular facets. Strain from faulty mechanics, therefore, must come on the articular facets and the joint capsule instead of on the body of the vertebræ. If this strain is great enough to cause inflammatory reaction and swelling of these ligaments and joints, the possibility of

narrowing the intervertebral foramina is very real. The spinous processes in lordosis may impinge on one another, and in extreme lordotic curves may act as a fulcrum and cause a stretching strain on the joints of the articular processes. If this backward strain was severe enough, these joints might be subluxed or even dislocated. Transverse processes may impinge on the wings of the sacrum, forming a true joint, or they may become firmly fused or sacralized. These changes will limit the possible amount of motion at this region of the spine in all directions and if, as one grows older, the curves of the spine become habitually increased, make more possible strains or irritations in this region.

Brown[3] summarized this phase in his statement that the fundamental principles were: 1, A joint which is used habitually in a position which has free motion in either direction has a small potential of injury. Such a joint has the so-called factor of safety motion. 2, A joint which has a small or no factor of safety motion has a definite potential of injury. 3, The best treatment for an injured joint is: first to correct the weight-bearing lines in order to regain the factor of safety motion, and then to be sure that function is carried out in good weight-bearing lines.

Danforth and Wilson[7] found that in only a small proportion of patients with sciatica could an etiologic factor of a general or constitutional nature, such as diabetes, syphilis, alcoholism, lead poisoning, and so forth, producing an inflammatory or degenerative change directly in the nerve be elicited. Likewise, vertebral tuberculosis and neoplasms, intrapelvic or extrapelvic tumors or inflammations producing pain either by direct pressure upon, or irritation of, the sciatic nerve at some point in its course or at its roots were comparatively rare. Essential or idiopathic sciatica (sciatic scoliosis) presented a clinical picture sufficiently striking to have earned for it a description as a disease entity. Goldthwait[9] was the first to investigate the problem from the anatomic and mechanical standpoint. He first called attention to the frequent occurrence of vertebral abnormalities, such as sacralization of the transverse process of the fifth lumbar vertebra and asymmetrical development of the posterior articulations, and pointed out the etiologic rôle which they, in combination with faulty body posture, might play in the production of sciatic pain. By their investigation, which included a series of dissections, they proved that the intervertebral foramen between the fourth and fifth lumbar vertebræ was always the smallest; that the fifth lumbar nerve root was usually the largest; the fifth nerve root was directly anterior to the posterior articulation between the fifth lumbar vertebra and the sacrum, and effusion in this joint might easily cause compression. Manipulation of the anatomic specimens demonstrated that hyperextension of the spine caused the posterior superior articular facets of the posterior joints to be driven upward toward the inferior intervertebral notches of the vertebra next above and in this way diminished the size of the intervertebral foramen exerting pressure on the nerve. Narrowing of the intervertebral disc between the fifth lumbar and first sacral vertebræ had the same effect.

Putti[23] considered sciatica as a symptom from the clinical standpoint.

In a diagram he illustrated the differentiation into neuritis, plexitis, funiculitis, ganglionitis and radiculitis, according to the area of the nerve-root involvement. In roentgenographic studies one is concerned only with funiculitis, because here only is pain found associated with anatomic alterations. The fourth and fifth nerves are those possessing the longest funicular portion of all those which constitute the lumbar plexus, that is they have the longest course through the intervertebral foramina. The funicular portion of the nerve does not lie within the arachnoid, but is only clothed by dura mater, and it is not bathed in cerebrospinal fluid. Around the funiculus there is a very rich venous plexus, which is much influenced by mechanical conditions outside the funiculus. This absence of arachnoid and a protective layer of fluid exposes the nerve to these outside mechanical influences and the surrounding venous plexus puts it at the mercy of any congestion or stasis that may occur in the neighborhood from any one of numerous causes. Variations in the direction of the articular facets in the joint between the fifth lumbar and first sacral vertebrae not infrequently alter the shape and reduce the capacity of the intervertebral foramina and these articulations may be the site of a localized arthritis, which itself may irritate the nerve trunk.

Mixter and Ayer[19] reported 34 cases of herniation or rupture of the intervertebral disc into the spinal canal. Pain was the first symptom in every case and it was for relief of pain that all except 2 sought relief; in the 2 cases disability was of prime importance. The pain was usually described as an ache in the low back, usually just to one side or the other, becoming paroxysmal on turning, stooping, coughing or sneezing, whereupon it would radiate outward over the buttock and down the back of the thigh, and at times the back of the leg also. Not infrequently the pain commenced in the midline and radiated down the back of both thighs, but unilateral distribution was the rule, even though symptoms had lasted many months. Pain in the perineum was also present in 3 patients. In only 1 was the pain referred to the anterior aspect of the thigh. In spite of great pain, little objectively determined sensory loss was the rule, and only rarely was bilateral saddle anesthesia obtained. This condition was first described in 1911 independently by Goldthwait in America and Middleton and Teacher in England; but these contributions seem to have been forgotten. In the meantime, reports of enchondroma or ecchondroma of the intervertebral disc began to appear and this interpretation continued in spite of the statement of their pathologist that the tumor on section looked like normal intervertebral disc. Mauric,[17] in 1933, from a study of the literature came to the conclusion that many of the so-called enchondromata and Schmorl's nodules (herniations of the nucleus pulposus) were identical. About the same time their clinical observations brought the same conclusion. The condition was rare compared with back strain, fracture, sacroiliac strain and the like. Examination of the spinal fluid and Roentgen ray examination with lipiodol were of the greatest importance in diagnosis.

Spondylolisthesis is another condition in which intractable low back pain brings the patient for examination. The first clinical observations were reported in the latter part of the Eighteenth Century. Kilian[15] (1853) gave it the name spondylolisthesis, a combination of the Greek words meaning slipping of the vertebra. Neugebauer[20] (1892) aroused interest in the subject, chiefly among obstetricians. There has been a considerable discussion as to the part of congenital separation of the neural arch, unilateral or bilateral, occurring through the laminæ between the superior and inferior facets, and trauma, in the occurrence of this lesion. Congdon,[6] in a study of a series of spines, found this anomaly in 5% of these and quoted Willis[26] as having elicited 4.8% in a similar study. From his observations Congdon felt that only a considerable separation would be discernible in the roentgenogram of the living subject. Other writers have asserted that all the results of anatomic and clinical study oblige one in most cases to look on injury as the cause. Primary fracture of the interarticular portion of the neural arch of the fifth lumbar was probably the most frequent. Congenital anomalies are at least a predisposing factor in many cases. Roentgenographically, an ovoid shadow appearing over the upper sacral segment in the anteroposterior projection is suggestive, a roentgenogram made in the lateral projection will reveal a subluxation of one vertebral body on the adjoining one, usually the fifth lumbar on the first sacral, a lengthening of the diameter from the tip of the spinous process to the anterior border of the affected vertebra over that of the contiguous one, and a "hump" in the outline of the neural canal at the point of involvement. A vertical line at right angles to the lower border of the vertebra above will pass anterior to the body of the dislocated vertebra in spondylolisthesis and through the body in the normal. Fixation by bone graft may be necessary for the relief of symptoms.

From the extensive literature covering the various phases of this interesting symptom some essays have been selected for this review that have not been specifically acknowledged, but these have been included in the bibliography to afford a more comprehensive study to those particularly interested in the subject as a whole.

C. G. Sutherland, M.D.

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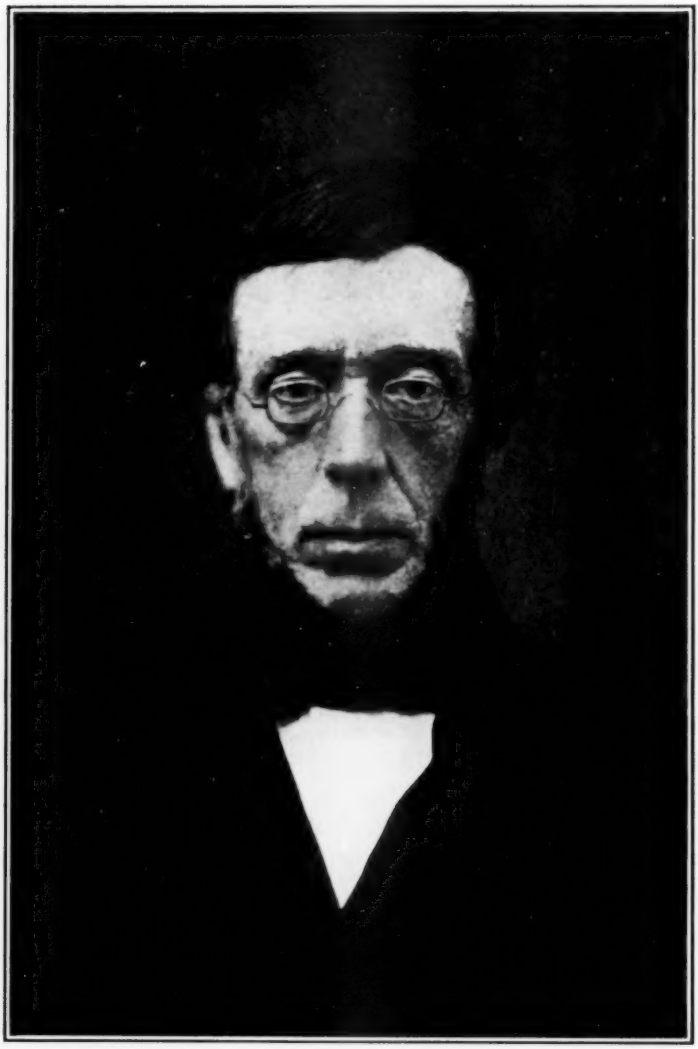
CENTENARY OF GERHARD'S DIFFERENTIATION OF TYPHOID FROM TYPHUS FEVER.

> "Thus, the triple lesion of the glands of Peyer, mesenteric glands and spleen, constituting the anatomical characteristic of the dothinenteritis of typhoid fever, although sought for with the greatest care, evidently did not exist in the epidemic typhus." (Am. J. Med. Sci., **19**, 302, 1837.)

Among the many noteworthy articles that have appeared in this Journal during the 127 years of its existence none is of greater importance than W. W. Gerhard's contribution "On the Typhus Fever, which occurred at Philadelphia in the Spring and Summer of 1836; illustrated by Clinical Observations at the Philadelphia Hospital; showing the distinction between this form of disease and Dothinenteritis or the Typhoid Fever with alteration of the follicle of the small intestine." As this notable landmark in early American medical literature appeared in this Journal in 1837 (February and August numbers), it is appropriate to commemorate its centenary at this time.

For the younger medical generation of today to whom typhoid fever has become almost a medical rarity, it must be difficult to visualize what an important step in medical progress this paper represents. Not only did this admirable clinico-pathologic study—in the best Louis tradition—segregate once and for all an important single disease, but it is perhaps of even greater significance from its effects in making a definite break in the hitherto confused mass of the continued fevers. This is not the place to go into any details of this complex situation that had lasted for centuries; nor is such action necessary, as the story has been well told elsewhere, especially by Dr. William H. Welch in the first Gerhard lecture of the Philadelphia Pathological Society (Proc., **28**, 42, 1925). We wish at this time merely humbly to commemorate the centenary of one of this Journal's most important articles.

The Editors.



WILLIAM WOOD GERHARD (1809-1872)